THE SURGICAL CLINICS OF NORTH AMERICA

OCTOBER 1978

PERSONAL PERSPECTIVES IN SURGERY

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SYMPOSIUM ON
PERSONAL PERSPECTIVES IN SURGERY

Rita McConn, Ph.D., *Guest Editor*

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Foreword

Amid the vast amount of medical and scientific papers written today, it is rare to find a piece of literature which relates information in a way which is not only instructive but enjoyable to the reader. The stereotypic style of current journals masks the individuality and feelings of the authors. Furthermore, the process by which clinical scientists work is rather different than commonly reported. Frequently the course of the work is directed by an incidental observation, stimulated by a chance conversation with a colleague, or by some strange accident of fate which brought together the right combination of people in the right place at the right time. No one would deny the influence of developments in the basic sciences and technology, while social circumstances, the advent of wars, and the dawn of new methods of warfare are factors which have also played a role in advances in medicine.

Within this century surgical medicine has reached the state of a fine art, but behind this progress lies buried many personal stories which have never been told. This issue of the *Surgical Clinics* is an attempt to collect some of these personal ventures into but a few of the many tributaries which flow into the Amazon of Surgery. The course charted and the travellers reflect my choice as guest editor. I hope you, the reader, enjoy them; perhaps it will stimulate one or two of you to chart, at some future time, a course into different waters. I am most grateful to W. B. Saunders Company for allowing me to launch this idea. My sincere thanks are due to the contributors who so kindly shared the story of their scientific travels, some of over more than half-a-century, while others relate of journeys currently in progress.

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Personal Reflections in Transplantation

*Thomas E. Starzl, M.D., Ph.D.**

The distortions produced by personalized versions of events are well known and particularly well illustrated by a number of articles in both the older and more recent transplantation literature. Consequently, the student of history will be well advised to consult less biased accounts by younger workers such as the catalogue of landmarks in renal transplantation provided by Groth of Stockholm after his study of the written record and after discussions with most of the workers actually involved in the work done from 1950 onward.[14]

Nevertheless, it may be interesting to describe some of the problems of human organ transplantation as they were perceived at the time of our first clinical trials 15 years ago and subsequently. This has been done first by briefly and incompletely sketching the background that had evolved to 1961, the year before the first consistent successes began to be obtained with kidney transplantation. Second, the great advances starting in 1962 are described in the second section. Finally, unsolved or incompletely resolved problems that still exist 15 years later make up the final section.

THE TWENTIETH CENTURY THROUGH 1961

The first known attempts at clinical renal transplantation by vascular anastomoses were made without immunosuppression between 1906 and 1923 with sheep, pig, goat, and subhuman primate donors.† None of the kidneys functioned and the human recipients died from a few hours to nine days later.

Yet, even in these first cases, some principles were clearly delineated despite the climate of ignorance in which the trials were conducted. The applicability of vascular suture techniques, the advisability of perfusion of the heterografts to remove donor formed blood elements, and even the possibility of using pelvic implantation sites were either acknowledged or actually practiced. The efforts to use animal organs were abandoned and no clinical renal heterotransplantations were tried again until 1963.

The first human-to-human kidney transplantation was reported in 1936 by Voronoy[51] who transplanted a kidney from a cadaver donor of B+ blood type to a recipient of O+ blood type in violation of what are now well accepted rules of tissue

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†The literature of these early heterotransplantation trials has been summarized in reference 41 (pp. 262–265).

transfer.[41] Nevertheless, a few drops of initial urinary excretion were observed. The patient's death 48 hours after transplantation was attributed to a blood transfusion reaction. The possibility that there would be an immune barrier to success was apparently not part of the consciousness of early clinicians. This realization awaited the classical studies of Medawar with rodent skin grafts which established the immunologic basis of rejection.[28]

In the 20 years following Voronoy's case, sporadic additional trials were made without the benefit of effective immunosuppression, as recounted 14 years ago by Goodwin and Martin[13] and more recently by Groth.[14] By 1951, Küss et al.[22] and other members of the French school of surgery[11, 40] had virtually standardized the procedure of kidney transplantation to the iliac fossa, anastomosing the renal to the pelvic vessels of the recipient in much the same way as is practiced today. Despite the lack of success with these early patients, other cases were soon reported from Chicago, Boston, Paris, Toronto, London, and Cleveland.* In the meanwhile, the technical soundness of renal transplantation to the pelvic site was unequivocally demonstrated by the identical twin grafting (isotransplantation) experience of Murray et al.[34]

By the middle of the 1950's, the total number of attempts at human renal homotransplantation had reached approximately 30 without any immunosuppression at all, or with adrenocorticotropic hormone (ACTH) or cortisone in a few patients of Küss et al.,[22] Dubost et al.,[11] and Hume et al.[20] Most of the homografts never had significant function, and those that did initially, usually underwent prompt rejection, as was reported particularly clearly by Michon et al.[30] There were three more or less clear exceptions to this generalization. Renal homografts inserted by Lawler,[26] Gordon Murray,[31] and Hume[20] and their colleagues were said to have excreted urine for several months before being rejected slowly. The life of Hume's patient probably was increased thereby by several months. The unexpectedly prolonged survival of kidneys in untreated recipients has been explained since by the loss of immunologic responsiveness that has been shown to accompany uremia.

In the meanwhile, the deliberate obtundation of immunologic reactivity became theoretically feasible when total body irradiation was shown to be immunosuppressive.[10, 25] After that, an intermediate era in renal transplantation was begun in 1958 by Joseph Murray and his associates at the Peter Bent Brigham Hospital using total body irradiation as the primary means to prevent rejection.[33] Although most of the recipients died, two patients are still alive who, in 1958, were given kidneys in Boston[33] and in Paris[15] from fraternal twin donors. Nevertheless, the great risks and highly unpredictable effectiveness of total body irradiation as the sole or main modality of immunosuppression made the undertaking impractical.

The transplantation explosion which eventually occurred from 1962 onward was dependent upon the use of drugs. The first and, as it turned out, most important class of agents was the steroids. The experimental basis for the use of steroids was laid in 1951 by Billingham, Krohn, and Medawar[3] with prompt confirmation by others. The second seminal development was the introduction of the thiopurine compounds, 6-mercaptopurine and its imidazole derivative, azathioprine. These agents were developed by Dr. George H. Hitchings and Gertrude Elion and their colleagues at Burroughs Wellcome and Company, Inc., Tuckahoe, New York, and found by them to inhibit hemagglutinin formation in mice challenged with heterologous red blood cells.[17]

In 1959, the action of thiopurine compounds in blunting the immune response to bovine serum albumin was reported by Schwartz and Dameshek[38] in the journal, *Nature*. By the time of publication, the authors had in press in *The Journal of Clinical Investigation* a second article which documented the effect of 6-mercaptopurine upon rabbit skin homografts.[39] Mean rejection time in 16 control animals was 6.8 days compared to 17.8 days in a group of 17 animals given 12 mg per kg per day of 6-mercaptopurine for 2 weeks, and the same dose every other day thereafter. In this important study, dose response curves were also defined. The work was presented at an international congress in London on September 7, 1959. The findings were promptly confirmed in another institution.[29] A further affirma-

*Annotation of the original articles is provided in reference 46 (p. 4, Part I).

tion of the antirejection qualities of 6-mercaptopurine came shortly afterward when it was tested by Calne[4] with the canine kidney model. Two mongrel dogs in this latter study survived for 21 and 47 days after renal transplantation from nonrelated donors and after bilateral recipient nephrectomy. The number of experiments were not stated nor were there controls. Further information was provided in later publications by Calne for 6-mercaptopurine and azathioprine.[5]

As recounted by Groth[14] a number of patients in Europe and the United States were given one or the other of the mercaptopurine drugs between 1959 and 1962, usually with a fatal outcome. However, two French recipients survived for prolonged periods of time. One who lived for 17 months was treated in 1960 by Küss and his colleagues[22] with 6-mercaptopurine after initial total body irradiation, and the other was managed similarly by Hamburger and associates[16] in January, 1962. By 1973, Hamburger's patient, whose donor was a cousin, had become the longest surviving non-twin recipient in the world. Murray et al.[32] reported the first patient in whom prolonged survival was achieved under primary immunosuppression with azathioprine alone; this recipient of a cadaver kidney lived for almost 2 years.[35] However, even well into 1962, there was little evidence that drug therapy would yield results substantially better than those obtained with total body irradiation. Such improvements would await the administration of drugs in combination (see next section).

My own involvement in transplantation began in the summer of 1958 at Northwestern University in Chicago. While a new method for one-stage hepatectomy was being developed in dogs, it was appreciated how easy it would be to replace the liver with a graft using a temporary portacaval shunt with or without an external bypass to decompress the blocked splanchnic and systemic circulations. At about this time, I had decided to remain in university work in preference to entering private practice and had spent several weeks in the medical library trying to decide upon some broad area of research in which to make an investment.

Transplantation seemed a worthwhile challenge, partly because of the deeply pessimistic attitudes that prevailed about the prospects of clinical organ transplantation in any except the most unusual cases such as those involving fraternal twins. Transplantation of the liver was especially appealing at that time because of its technical challenge.

Another factor that gave the liver special interest was speculation by Dr. Jack Cannon of Los Angeles that the liver played an important role in rejection. Because of this, Cannon, who was the first to attempt liver replacement,[7] apparently hoped that a hepatic homograft might suffer a different fate from that of other transplanted tissues since it presumably would not contribute to its own repudiation. As it turned out the liver has seemed to be less susceptible to rejection than any other major organ but for reasons that are still not understood.[42] Between 1958 and 1962 in the experimental liver transplant program which I established in Chicago, a brief attempt was made to irradiate both the graft and the recipient; prolongation of graft survival was not obtained.

THE KIDNEY FROM 1962 ONWARD

The kind of laboratory research with steroids, 6-mercaptopurine and azathioprine mentioned above was applicable in one way or another to organ replacement in man, but the connection was not straightforward. In occasional dogs a protracted life proved possible after renal transplantation with the use of steroids,[53] 6-mercaptopurine,[37] or azathioprine[5, 36, 41] as the sole immunosuppressive treatment. In man occasional similar successes were occasionally achieved solely with 6-mercaptopurine or azathioprine as was mentioned earlier. Nevertheless, the consistency with which really long-term survival was obtained was poor. The obvious reason was that complete control of rejection was rarely achieved.

Thus, both the animal data and the initial clinical experience discouraged further trials. The most important development which made immunosuppression practical was the discovery of the way in which azathioprine and prednisone could be advantageously used together. There were essentially no preceding laboratory data to indicate that the benefit with this now universally accepted combination of

agents would be as great as proved to be the case. Indeed, the first publication on experience in animals[27] was a belated confirmation of the far more convincing observations already made in humans.[45]

Furthermore, it is difficult even in retrospect to ascribe priority for standardization of azathioprine-steroid therapy to any single authority or transplantation group. What is clear is that by early 1963 the two drugs were being used together in one way or other and with varying degrees of conviction about their synergism for the prevention or reversal of renal homograft rejection in at least one British[52] and three American centers.[19, 35, 45] Since then, variations of these regimens have been adopted throughout the world.

The way in which our own initial efforts in renal transplantation evolved was as follows. Shortly before I came to the University of Colorado in late 1961, a 27 year old man suffering from terminal renal disease was seen at the Denver Clinic by Dr. Philip Clarke. Dr. Clarke discussed the case with Dr. William R. Waddell, who had come to Colorado in July, 1961, as Professor and Chairman of the Department of Surgery. After my arrival at Christmastime, 1961, Dr. Waddell arranged for me to see the patient and because of my interest in transplantation he asked me to organize an interdisciplinary treatment team. Fortunately, the recipient had an identical twin. The transplantation was carried out on March 27, 1962. Dr. Robert Brittain performed the donor nephrectomy. I performed the recipient operation with the assistance of Drs. Oliver Stonington, Richard J. Sanders, and William R. Coppinger.

While this first patient was still recuperating, a second recipient who did not have the advantage of a genetically identical donor was admitted to the hospital in renal failure. The month was May, 1962. Chronic dialysis was not yet a well established form of treatment. On acute intermittent hemodialysis the access vessels were rapidly consumed in this and other early patients. At the same time, desperate efforts to develop effective immunosuppressive treatment with total body irradiation and azathioprine were carried out in the laboratory of the Denver Veterans Administration Hospital. Completely acceptable results in dogs could not be by either irradiation or azathioprine alone or, for that matter, when they were used in combination.

Nevertheless, the decision was made to proceed with transplantation of this 12 year old patient since the prospects of further dialysis treatments were dismal. The plan was to give 300 R total body irradiation preoperatively, 100 R more postoperatively, and to supplement this treatment with azathioprine as the bone marrow depression recovered. The treatment schedule was similar to that used by Murray[33] and Hamburger[15] for their fraternal twin cases. If rejection occurred steroid therapy was planned.

The course of that first patient is summarized in Figure 1. The kidney which was donated by the boy's mother functioned well initially but after two weeks a severe rejection developed in spite of the fact that there were virtually no circulating white blood cells. The BUN rose to more than 75 mg per 100 ml and the creatinine clearance fell to about 5 ml per minute. Prednisone in daily doses of as high as 150 mg was added and daily doses of azathioprine were cautiously added about two weeks later.

Although the rejection was thereby reversed with survival of the patient to the present time, the frightening experience with total body irradiation and consequent bone marrow depression convinced us that the irradiation should be omitted on the next occasion. In the following 44 cases[41] azathioprine was started shortly before operation and continued in the maximum doses that were thought to be possible without the production of leukopenia. Prednisone was withheld until graft repudiation had clearly started. In retrospect, the most important advantage of withholding steroids until a specific indication was that the features of rejection and host-graft adaptation, as well as the influence of drug therapy on these processes (see below) could be delineated with some precision. The greatest disadvantage was that the rejections which developed under treatment with azathioprine alone were sometimes very severe and difficult to reverse with delayed steroid therapy. It was found that their incidence and seriousness were reduced if prednisone was given from the beginning.[41] Consequently, it has been our policy since December, 1963, to immediately treat virtually all recipients of organ homografts with predni-

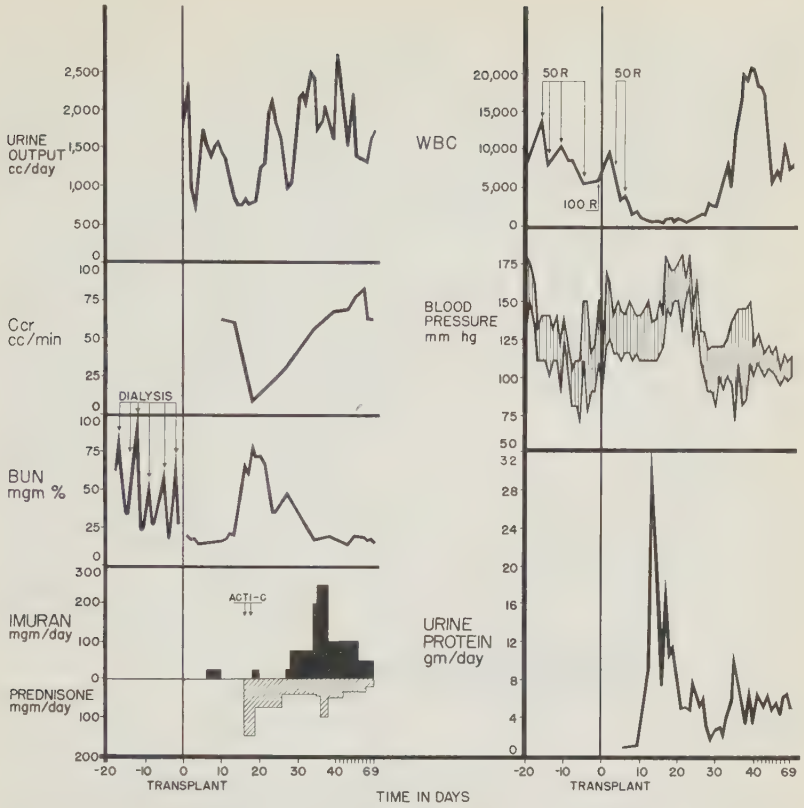

Figure 1. Rejection crisis in patient (LD 1) treated initially with total body irradiation (400 R). Note transient oliguria, depression of creatinine clearance, and elevation of blood urea nitrogen, blood pressure, and urinary protein excretion. The changes were all reversible. The patient previously had undergone bilateral nephrectomy, splenectomy, and thymectomy. R, dose total body irradiation; Acti-C, actinomycin C (each arrow equals 200 μg of actinomycin C administered intravenously). Imuran is synonymous with azathioprine. These general events of rejection have occurred despite treatment with all the therapeutic regimens used at this and other centers since 1962. (*From* Starzl, T. E., et al.: The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg. Gynecol. Obstet., *117*:385, 1963, with permission.)

sone and azathioprine (sometimes cyclophosphamide has been used instead of azathioprine), to which in recent years heterologous antilymphocyte globulin (ALG) has been added in a triple drug program.

By the spring of 1963, the practical possibilities of clinical renal transplantation had already become obvious from observations of our first patients. One reason was the repeated demonstration that rejection was a highly controllable and reversible process. The first report to this effect began as follows:[45]

> "Because of the high failure rate after renal homotransplantation, there has been an air of pessimism concerning the possibility of long term function of the grafted kidney. The immunologic processes subserving rejection are generally thought to be so powerful and persevering that consistent success cannot be expected with the use of any of the currently available methods of antirejection therapy.
>
> "Recent personal experience in caring for patients with renal homografts has resulted in alterations in many of our preconceived notions concerning the management of such patients. It has led to the beliefs that the

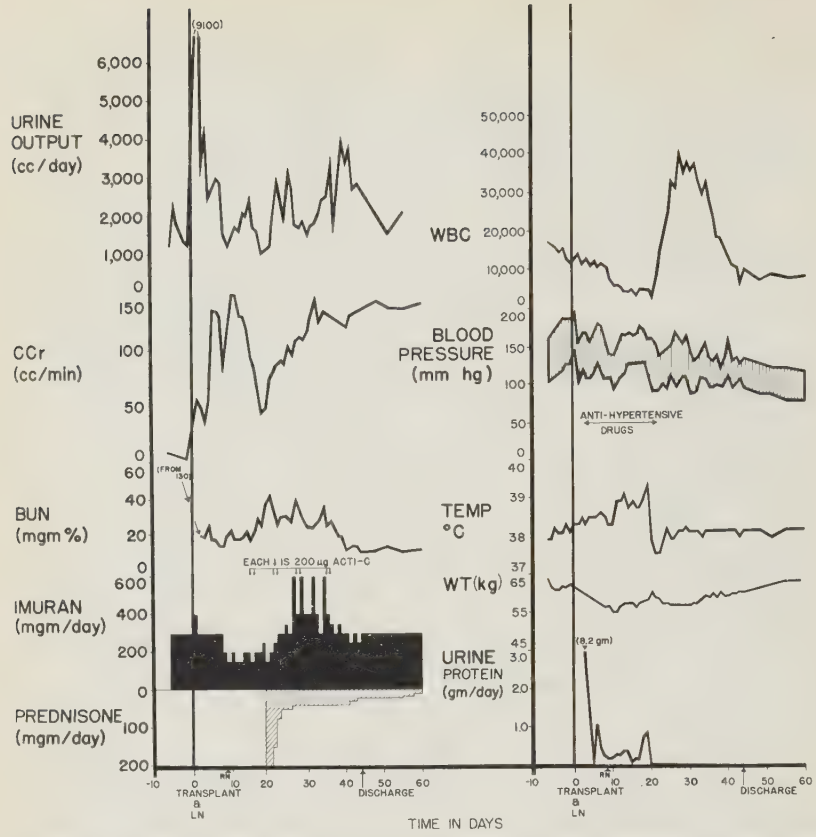

Figure 2. Classic rejection crisis in patient (LD 6) treated with drugs alone. Deterioration of renal function began 19 days after transplantation. All stigmata of rejection are present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. Acti-C, actinomycin C; LN, left nephrectomy at time of transplantation; RN, Right nephrectomy. Imuran is synonymous with azathioprine. (*From* Starzl, T. E., et al.: The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg. Gynecol. Obstet., *117*:385, 1963, with permission.)

rejection process can almost never be entirely prevented, but that its effects can be reversed with a high degree of regularity and completeness. Furthermore, the subsequent behavior of patients who have been brought through a successfully treated rejection crisis suggests the early development of some degree of host-graft adaptation, since the phenomenon of vigorous secondary rejection has been encountered only once."

In that series there were 10 patients treated in late 1962 and early 1963. In seven, including the first one treated with irradiation and mentioned earlier, clear cut rejection of variable intensity occurred from 4 to 34 days after operation (Fig. 2), in one case actually leading to anuria. In each instance, the process was reversed by the addition of massive doses of prednisone to the pre-existing therapy with azathioprine (Fig. 2). Three of these seven patients are still alive 14 or more years later and are now among the longest living recipients of non-twin homografts in the world. After the remarkable effectiveness of steroid therapy in this situation had been established from our own experience, but before our findings were published, it was learned that the same kind of observation had been made by Goodwin and his associates[12] in a young woman who ultimately died of sepsis 144 days after receipt of a maternal homograft.

The reversibility of rejection in these patients was only one of the features which established the clinical feasibility of organ transplantation. The quantities of adrenal corticosteroids necessary to achieve reversal were often too large to be compatible with long survival of the recipient if continued indefinitely. Fortunately, another event of equal practical importance transpired coincidentally with the reversal of rejection or shortly afterward. With the passage of time, the need for intensive therapy usually diminished both in patients who did and those who did not pass through a clinically evident rejection. Thus, the patient whose course is depicted in Figure 2 had returned within five months after transplantation to treatment only with azathioprine, a drug which at the outset did not prevent the onset of a moderately severe rejection. An ultimate similar reduction in drug requirement is seen today in almost all new successfully treated recipients and it is probable that some patients could eventually have all therapy stopped. In our laboratory, we have had dogs live for 10 to 12 years after being given treatment with immunosuppressants only for the first four postoperative months.

The foregoing phenomenon of graft acceptance is not understood (see discussion in reference 42, p. 229). However, there is little reason to doubt that a homograft becomes more or less privileged if it can be kept alive through the initial onslaught of rejection. This fact is at least partly responsible for the shape of life survival curves after renal homotransplantation in that the preponderant mortality is in the first few postoperative weeks or months when stringent immunosuppression is required. It has strongly influenced the way in which new therapeutic agents such as heterologous antilymphocyte globulin (ALG) have been used clinically, and it has been a prime stimulus for the extension of transplantation techniques to organs other than the kidney in which both reversal of rejection and "adaptation" are not very different from what they are with the kidney.

In any event, the numbers of successful cases grew rapidly during the spring and summer of 1963. By the first week of September, 1963, when an international meeting was convened at the National Research Council, 2101 Constitution Avenue, Washington, D.C., to consider the past and future of renal transplantation, our Colorado series of kidney recipients was up to 27. In preparation for this meeting on September 26 and 27, 1963, the 2½ × 3½ foot wall flow sheets from all of these patients were gathered together with the aid of Tom Marchioro, now Professor of Surgery at the University of Washington, Seattle, and bound between soft leather covers like Egyptian scrolls. These were carried by Bill Waddell and me to Washington.

I remember the surprise, if not incredulity, that greeted our report of a very high survival rate (20 of the 27 patients were alive) with so many examples of essentially normal renal homograft function. The book of flow sheets promptly found itself on the center conference table under close scrutiny. The recorded proceedings of the meeting contained much lively, provocative and friendly discussion which would have made interesting reading, but very little of the spirit of that meeting survived to make its way into print.[18]

On the last evening of the conference, Dave Hume of Richmond and Kendrick A. Porter of London came to my hotel room. We spent almost all the night going over each of the Colorado cases. As soon as the meeting finished, Porter and Roy Calne came to Denver where a further exchange of information and ideas took place.

Realizing the unique value of our cases, I had already started to write a book based on the University of Colorado clinical material. Before he left Denver, Ken Porter had agreed to prepare a section on the histopathology of renal homotransplantation. His chapter became a monograph in its own right (see reference 41, pp. 299–359) to which surprisingly little has been added in the intervening years. Porter and I have maintained a fruitful collaboration since then.

By the time the book was finished the following May, the series had increased to 64. Today with follow-ups of 13 to almost 15 years, about one-half of that original group are still alive. A great number of original observations were made possible by the chance to watch this bellwether group of patients and those were summarized in the book. The operative techniques for renal transplantation in adults as well as children were standardized. The rules of acceptable transfer of tissues between donors and recipients of different blood types were established, and it was shown that violation of these rules could lead by the action of preformed recipient an-

tibodies (in this case isoagglutinins) to what later became known as "hyperacute rejection." The first widely used techniques of organ preservation were introduced, consisting of cooling of the excised organs by infusion with cold solutions. More sophisticated methods of preservation, including cadaveric whole body perfusion, were introduced. The requirements and techniques of infectious disease control were standardized. A limited, informative, but ultimately unsuccessful trial of renal heterotransplantation using baboon kidneys was undertaken. A comparison of the fate of these baboon heterografts with that of Reemtsma's chimpanzee heterotransplantations show that the chimpanzee would be a better donor if animals are used for this purpose in the future.

By the spring of 1964, the basic care of kidney recipients under double drug immunosuppression had been standardized in much the mold that is so familiar today. Further developments have occurred. Most importantly, the supply of high quality organs has been greatly increased by the wide acceptance of irreversible brain injury as the ultimate definition of death rather than the cessation of heartbeat.[9]

The importance of these changes in social and legal attitudes has been amplified by research in organ preservation. In 1967, Belzer and his associates in San Francisco described ex vivo perfusion methods with plasma derivatives that allowed the preservation of kidneys for two or three days.[2] Not long after simple flush techniques using cold electrolyte solutions of intracellular composition (containing high potassium and high magnesium) were introduced that allowed successful refrigeration for 24 to 48 hours.[8] With these improvements in organ preservation, renal transplantation became an elective undertaking in comparison to the urgent conditions which had been necessary before.

In tissue typing, there were great expectations in the middle and late 1960's. The first retrospective as well as the first prospective attempts at HL-A tissue typing in kidney recipients were inaugurated in a collaboration with Dr. Paul Terasaki of Los Angeles.[50] Unfortunately, the fuzzy correlations of HL-A matching and the outcome in all except perfectly matched sibling cases indicated that the tissue typing issue was much more complex than had been appreciated. The use of tissue matching to identify good sibling combinations has been useful. But from a practical standpoint the most important matching procedures today are the direct crossmatches which avoid placing a kidney into a recipient who possesses preformed antigraft antibodies. The first lessons about the harmful effects of preformed antibodies were learned with blood group mismatches in which antired cell isoagglutinins triggered hyperacute rejection.[41] Not long after, the devastating effects of preformed cytotoxic antibodies were described by Terasaki et al.[49] and Kissmeyer-Nielsen et al.[21]

In 1966, we introduced what has since been called a triple drug program of immunosuppressive therapy adding antilymphocyte globulin (ALG) to azathioprine and prednisone. ALG consists of antibodies raised in animals against human lymphocytes. The regimen of ALG which was used in man was guided by several general conclusions that emerged from the experimentations with large animals in our laboratories and elsewhere.[24, 43] These can be summarized as follows: (1) ALG had potent but imperfect immunosuppressive qualities when used alone; (2) with continued administration of the heterologous serum derivatives there was a highly significant risk from a variety of foreign protein reactions; and (3) ALG could be used effectively and probably with increased safety in combination with other drugs. Each of these factors contributed to the initial decision to employ heterologous ALG as an adjuvant agent added to therapy with azathioprine and prednisone and to limit its use to the first four postoperative months. It was hoped that the predictability and safety with which homograft rejection could be prevented would thereby be improved and that the hazards of immunologic reactions to the serum products would be accordingly reduced with the efficient level of immunosuppression to which all three agents would contribute.

These basic tenets have been used in all the modifications of the triple agent program that have been used since that time. The original trial of the ALG was given intramuscularly but the intravenous route is usually used now. Questions are incompletely answered about the best kind of lymphoid antigen and the most appropriate animal in which to raise the antilymphocyte antibodies as well as the

Table 1. *Experience with Renal Transplantation at the University of Colorado, 1962–1975*

SERIES	NO. OF CASES: Related	NO. OF CASES: Unrelated*	DATES	FOLLOW-UP TO AUG 1976 (YEARS)	MAIN FEATURE
1	46	18	Nov 1962 to Mar 1964	12⅓–13¾	Azathioprine/prednisone; good risk
2	25	23	Oct 1964 to Apr 1966	10⅓–11⅝	Azathioprine/prednisone + typing; good risk
3	60	17	June 1966 to Feb 1968	8½–10⅛	Azathioprine/prednisone/ ALG; good risk
4	122	15	Mar 1968 to Mar 1971	5½–8½	Azathioprine/prednisone/ ALG; all risk
5	44	28	Mar 1971 to Aug 1972	4–5½	Cyclophosphamide/prednisone/ALG; all risk
6	65	49	Aug 1972 to Aug 1974	2–4	Azathioprine/prednisone/ ALG; all risk
7	27	17	Sept 1974 to Aug 1975	1–2	Azathioprine/prednisone/ ALG; all risk

*Since late 1965, all unrelated kidneys have come from cadavers. Before then, nonrelated volunteer donors were used.

correct dose and timing of the ALG (see discussion in reference 42, pp. 207–216). For that matter, a number of authors have contended that ALG does nothing in improving immunosuppression that could not be achieved equally by the clever manipulation of steroid and azathioprine doses.

In spite of this skepticism, most of the reports of controlled studies with ALG have shown a higher rate of kidney survival, fewer rejections and at least equal patient survival. At the International Transplantation Society meeting in September, 1976 (New York City), there was a stronger consensus than at any time in the preceding decade that ALG was a useful clinical adjunct.

The only other major immunosuppressive agent that has been used extensively has been cyclophosphamide. In 1970 and 1971 we showed that in large series in which cyclophosphamide replaced azathioprine as part of a double or triple drug program, the results were essentially the same with either drug.[48] Although the results were no different from those obtained with azathioprine, we have since returned to the routine use of azathioprine because of our much greater experience with it and because of our high degree of satisfaction with its use.

Table 2. *Actual Survival at One Year and Thereafter in Patients Given Primary Related Grafts from 1962 to 1975*

SERIES	NUMBER OF CASES	PER CENT SURVIVAL: 1 Year	2 Years	4 Years	8 Years	10 Years
1	46	67	65	61	57	52
2	25	64	64	52	40	40
3	60	92	88	78	67	
4	122	76	73	68	—	
5	44	86	80	74	—	
6	65	77	75	—	—	
7	27	89	—	—	—	

Table 3. *Actual Survival at One Year and Thereafter in Patients Given Primary Nonrelated Grafts from 1962 to 1975*

SERIES	NUMBER OF CASES	PER CENT SURVIVAL				
		1 Year	2 Years	4 Years	8 Years	10 Years
1	18	33	22	17	11	11
2	23	52	43	30	17	13
3	17	82	76	41	29	—
4	15	80	80	80	—	
5	28	75	75	61	—	
6	49	82	71	—	—	
7	17	94	—	—	—	

The immunosuppressive protocols developed at the University of Colorado and the patients treated are listed in Table 1. The results of this experience brought up to date to August, 1976, were presented at the 1976 meeting of the International Transplantation Society, have been recently published, and are summarized in Tables 2 and 3. The greatest improvement in recent years has been survival after cadaveric transplantation (Table 3) and, in turn, this is explained by a greater willingness to abandon an initial homograft and to consider return to dialysis or retransplantation. At the present time, recipients of either related or unrelated homografts are surviving for one year at about an 80 to 90 per cent rate and about three-fourths are still alive at the end of 4 years.

CLINICAL LIVER TRANSPLANTATION

Looking back at the Colorado scene of the early 1960's, it was inevitable that transplantation of the liver would be performed. Optimism was high because of the success of double drug immunosuppression in controlling renal homograft rejection. The assumption was made that the same therapy would be applicable for other organs, a view that was proved correct both in animals and man.[42] Finally, the ability to carry out liver transplantation had been assiduously developed in research involving hundreds of dogs during the preceding 5 years and was known to be within our technical capability. Thus, a policy decision was made in early 1963 to proceed with orthotopic liver transplantation, an operation which requires removal of the diseased native organ and its replacement with a cadaveric graft (Fig. 3).

The first 4 attempts were made in 1963 on March 1, May 5, June 24, and July 16. A fifth patient was treated by Francis Moore in Boston on September 16, 1963, followed by another in Denver on October 4, 1963 (all early cases in Denver and elsewhere are catalogued in reference 42, pp. 530–532).

Our first recipient bled to death during the operation; the other 4 first Denver patients survived operation but died from 6½ to 23 days later. Success was nearly achieved in some of these cases.[44] For example, our second patient, a 48 year old male with cirrhosis and a hepatoma, was in remarkably good condition postoperatively. He died 22 days later of systemic and pulmonary infection. At autopsy there were no serious complications in the abdominal cavity. The liver had no unequivocal findings of rejection. Biliary duct reconstruction with choledochocholedochostomy over a T-tube was satisfactory (Fig. 3). Portions of both lungs were necrotic. The pulmonary arteries contained multiple old clots. Apparently, these were deposited at the time of operation from a plastic bypass tubing that had been used to return blood from the vena caval and splanchnic venous pools while these systems were obstructed during the intraoperative anhepatic phase. Ironically, it was later proved that such temporary bypasses are unnecessary because of the well developed venous collaterals in end-stage liver disease.[42]

The series of consecutive early failures caused a moratorium of 3 years to be declared on further cases. Only one more patient was treated at our center until the summer of 1967. The justification to then start another series came from experience with the triple drug immunosuppressive program (including ALG) which by then seemed to be helping the kidney recipients. On July 23, 1967, the chance presented to treat a 1½ year old girl who had a hepatoma. She lived through the operation of liver replacement and for 13 months afterward before finally dying of widespread tumor metastases. Each of the next 8 recipients lived for at least 2 months postoperatively, and 3 of these 8 lived for more than one year with the longest survival of 29 months and 16 days.

The first 25 liver recipients in the Colorado series eventually provided the experience for a text of liver transplantation.[42] Five of these 25 patients lived a year or more. The feasibility stage of human liver transplantation had been passed, but with a one-year mortality of 80 per cent, widespread exploitation of the procedure was a long way off.

Nor was there a quantum improvement in the succeeding 7 years. The patients surviving for one year in the second, third, and fourth groups of 25 patients each were only 6, 8, and 9, respectively. However, one of these recipients is now 7⅓ years postoperative and a total of 6 have lived more than 5 years; 5 of these 6 are still alive.

During a sabbatical leave in 1975 and 1976, I had an opportunity to live in London and to work with Professor K. A. Porter whose collaboration was described earlier in this article. Together, we reviewed the first 93 cases of orthotopic liver transplantation and tried to recatalogue the main reasons for failure. Our conclusions were that:[47] (1) uncontrolled rejection was a relatively uncommon cause of mortality; (2) technical mistakes and mechanical problems with the homografts accounted for the greatest numbers of deaths; and (3) if the complications were of duct reconstruction they frequently caused untreatable infections.

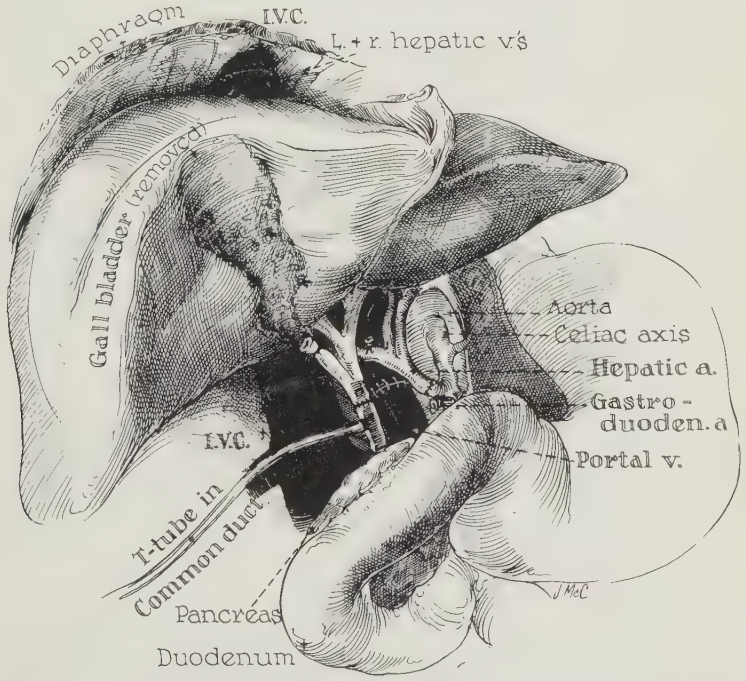

Figure 3. Orthotopic liver transplantation with biliary duct reconstruction by choledochocholedochostomy after cholecystectomy. Other acceptable techniques of biliary reconstruction involve anastomosis of the homograft gallbladder or common duct to a Roux-Y jejunal limb.

Better management guidelines were developed based on more accurate diagnosis with emphasis on frequent needle biopsies and transhepatic cholangiography, avoidance of overimmunosuppression while using the triple drug therapy, and better technical performance at the original operation. The most fundamental technical adjustment was to perform biliary duct reconstruction with choledochocholedochostomy over a T-tube stent (Fig. 3), or by anastomosis of a Roux-y jejunal limb to the graft gallbladder or common duct. The various changes were completed and standardized by late spring, 1976.

Since then, 19 more patients have had liver replacement. With follow-up periods of 3 weeks to 12 months, 14 of the 19 recipients are alive. The 4 postoperative deaths have been due to rejection (one example), inability to revascularize the liver due to recipient portal vein thrombosis (one example), subhepatic infection with erosion into the hepatic artery (one example), bone marrow depression with pneumonitis (one example), and uncontrollable heart failure (one example). The expectation now is that more than one-half and possibly as many as two-thirds of the modern day liver recipients are going to survive to the one-year mark. The same improvement in recent results has been noted also by Calne and Williams working in England.[6]

One of the major by-products of liver transplantation has been new insight about the effect of portal blood and its so-called hepatotrophic constituents on liver structure, function, and the capacity for regeneration. This new area of research was opened during inquiries into the optimum means of revascularizing auxiliary liver homografts while leaving the native organ in place.[23] The essence of portal hepatotrophic concept is that the liver is controlled or influenced profoundly by hormones coming from the venous effluent of splanchnic viscera into the portal vein. Insulin is the most influential of these hormonal factors, although not the only one. From a practical point of view and as it relates to transplantation, the implication is that the portal vein of an auxiliary liver should be supplied with splanchnic venous blood if it is to have an optimal chance of survival.

Auxiliary liver transplantation was first attempted in humans by Absolon et al.[1] and was also given a brief trial at our center.[42] The only person to definitely benefit from this procedure so far has been a child cared for by Dr. Joseph Fortner of New York who is now 4 years after auxiliary transplantation for biliary atresia. We have not performed this operation for several years.

OTHER ORGANS

The dramatic extension of basic transplantation concepts to heart replacement, lung transplantation, and pancreatic transplantation are well known and beyong the scope of this article. We have carried out 7 heart transplantations with the longest survival of 29 months. Several years ago, a decision was made not to do more cardiac cases since our trials did not add to the developmental efforts of the Stanford team headed by Norm Shumway and Ed Stinson.

Unresolved Problems

The great wave of successful renal transplantations in the early 1960's and the prompt demonstration that extrarenal organs could also be transplanted in humans led to a mood of exhilaration seldom tempered by a cautionary note. Although the situation was acknowledged to be imperfect, it was widely believed that new and fundamental developments with which to correct any deficiencies were close at hand. Indeed, as was already stated, many advances were subsequently made in surgical techniques, in organ preservation, and in understanding the complexities and limitations of tissue typing.

However, growth arrest has occurred in the one area that gives transplantation uniqueness and that is central to a myriad of complications which organ recipients must still face. The main problem area remains immunosuppression and from this combined with the impracticality of donor selection by tissue typing stems two therapeutic deficiencies.

First, the predictability of treatment is imperfect. A reasonably accurate prognosis can be offered only to recipients of perfectly matched sibling kidneys. But

even here there is an occasional unexpected graft loss from rejection that cannot easily be explained despite intensive retrospective study. Using relatives other than perfectly matched sibling donors, the predictability of rejection control is substantially less. When cadaveric organs are transplanted, some patients have uncontrolled rejection, others have no difficulty at all, and about half are intermediate between these extremes. Although the exact success rate after cadaveric kidney transplantation is influenced to some extent by the inclusion or exclusion of candidates who have a high risk because of advanced age, coincident disease, or other factors, kidney survival at one year using any of the presently employed regimens is seemingly more or less fixed at about 50 to 70 per cent in all the world's great transplantation centers.

The second general defect is related to the first. At the present time, even patients who eventually achieve a perfect transplant result often must first pass through a postoperative period of significant morbidity. The requirement for intensive immunosuppression is greatest early after transplantation. Because the steroids are the only highly dose-maneuverable component of the immunosuppressive regimens presently employed, the intensification of therapy translates inevitably into larger quantities of prednisone. If high-dose steroid therapy can be avoided or kept to a brief duration while at the same time maintaining good homograft function, the result is apt to be spectacularly successful If steroids are needed chronically, their well-known side effects depreciate the value of post-transplantation life or may threaten survival itself if the doses are too high.

Although the drug combinations that include azathioprine, prednisone, cyclophosphamide, and ALG have evolved into well standardized double- or triple-drug cocktails that have been used the world over, all are variations on the same theme. Further small adjustments in dosage and schedule are not going to correct the deficiencies of transplantation just mentioned. Some drastic changes in approach are going to be needed. The objective is a foreshortening of the graft acceptance process, so that the transplant passes through the danger period in a few days instead of a few weeks or months.

The first step to accomplish this is to acknowledge that our present methods of treatment represent only a halfway station toward an acceptable final regimen. Some kind of tolerance induction or the effective use of enhancement procedures might be made easier if better drugs were found but no hint of a breakthrough in any of these areas is evident at present.

Nevertheless, a high order of patient service can be provided today with renal transplantation despite the limitations of immunosuppression. The reason is that it is so easy to return patients to chronic dialysis if too much immunosuppression is required to retain homograft function. The same is not true for the liver, heart, and lung, for which artificial organ backup is not available. Using these organs, transplant and patient survival are nearly synonymous.

With the heart, the transplantation itself presents no troublesome technical problems, and in Shumway's magnificent series the life-survival curve reflects very accurately the ability to control cardiac rejection. The one-year survival has edged up to above 50 per cent in the Stanford series. As described earlier, a similar steady improvement has been seen with the immunologically easier but technically more difficult liver. Very little work is now going on with the lung.

With both the liver and lung, it is unlikely that a clear distinction between technical, infectious, and rejection problems will be possible until a much more reliable method is available for the promotion of graft acceptance. Then if something goes wrong it can be assumed that rejection is not the cause. Today the obverse assumption that rejection is responsible must always be made.

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Perspectives in Cardiac Surgery with Personal Reflections

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The extraordinary development of cardiac surgery during the past few decades has sometimes astonished even active participants in the field. This is not surprising when one reflects that less than a century ago the heart was considered beyond the realm of the surgeon's skill. Since heart disease is the major cause of death in modern times, it is appropriate that surgeons have risen to meet the challenge. In this country approximately 200,000 heart operations are performed annually; two-thirds of these require cardiopulmonary bypass.

The brief history of heart surgery dates back to the turn of the 20th century. While some rather crude operations had been done, such as drainage of pericardial effusions or collections of sepsis, the first direct surgery upon the heart was done for perforating injuries. In 1896 the German surgeon Rehn[40] successfully sutured a stab wound of the heart. Meanwhile, several other surgeons also accomplished the same rather incredible feat. Fifty years later, surgery of cardiac trauma provided another major stimulus for development of modern surgery when, during World War II, Dwight Harken of Boston[30, 31] reported his remarkable experience in removing foreign bodies from the heart by a variety of ingenious techniques. Harken's intrepid action in this endeavor demonstrated the durability of the recuperative powers of this organ.

Although external drainage of suppurative disease of the pericardium had become widely used, it was Delorme and Schmieden[17, 44] who first operated successfully upon patients with chronic constrictive pericarditis. In the 1920's Edward Churchill of Boston[11] and others in this country were soon to follow his lead. Subsequently, Claude Beck of Cleveland[4] described the findings in Pick's disease (constrictive pericarditis) known as Beck's triad—small quiet heart, increased venous pressure, and ascites.

One of the first recorded attempts to correct congenital heart disease was made by John Munro of Boston.[38] Observations in cadavers led him to believe that a patent ductus arteriosus could be closed surgically. He also described a technique which could be done through the mediastinum without crossing the pleural space. The first successful surgical repair of a ductus was made by Robert Gross of Boston[27] more than 30 years later. Oswald Tubbs of London[52] later reported successful closure of a patent ductus in a patient with subacute bacterial endocarditis, which was one of the first recorded cures of endocarditis during the pre-antibiotic era. Further advances in the treatment of congenital anomalies were soon to follow. Blalock and Park in 1943[7] reported their animal experiments in which coarctation of the aorta was produced and then corrected by using a bypass with the left subclavian artery. Soon thereafter Clarence Crafoord of Stockholm[14] and Gross of Boston[26] reported their technique of resection with end-to-end anastomosis. Subsequently, Gross made a significant additional contribution in the development of techniques for homografting the aorta. This method, in which Charles Hufnagel of

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Washington, D.C.[28] was a collaborator, made possible later developments in vascular surgery using freeze-dried homografts and fabric grafts later.

As cardiac surgery was evolving, Cournand[13] introduced his technique of cardiac catheterization stimulated by Forssmann's research,[21, 22] which began when he introduced a catheter into his own heart! Another significant diagnostic technique in the use of angiocardiography was introduced during those early years by Robb and Steinburg of New York.[41]

Among the most stimulating and imaginative advances in the treatment of congenital heart disease came when Alfred Blalock and Helen Taussig of Johns Hopkins Hospital in Baltimore[8] introduced their technique of systemic-to-pulmonary artery shunts for tetralogy of Fallot. The improvement in these hopelessly incapacitated and cyanotic infants was dramatic, and cardiac surgeons began a frenzy of activities. Application of physiologic principles to cardiac surgery was then introduced, and many others sought to use these concepts as indirect means of solving cardiac deficiencies. For example, Bland and Sweet of Boston[6] developed an anastomotic procedure between the right superior pulmonary vein and the superior vena cava to relieve the pressure in the left atrium, produced in mitral valve disease. Similar anastomotic techniques were attempted for transposition of the great vessels and other congenital and acquired lesions, but none achieved the success of the Blalock-Taussig procedure. A technical modification was introduced by Willis Potts[39] who developed a method of anastomosing the left pulmonary artery to the descending thoracic aorta by a side-to-side technique. Later Waterston of London[53] and, independently, our group developed an additional modification of Blalock's operation by anastomosing the ascending aorta to the right pulmonary artery. But indirect attacks upon cardiac disease had severe limitations.

The surgery of acquired valvar stenoses was suggested at the turn of the century by Brunton and Samways of England.[10, 43] The first direct attack on the lesion, however, was made by Elliott Cutler of Boston with his colleagues, Samuel Levine and Claude Beck.[15] These surgeons introduced cutting instruments into the mitral valve in order to excise scarred, calcified, and stenotic tissue. Unfortunately, when they were successful in completing this procedure, significant mitral regurgitation resulted. Meanwhile, in London, Henry Souttar[49] performed the first finger fracture valvuloplasty. While there is some question about the true nature of the mitral lesion in his case, the technique of digital dissection through the left atrial appendage was later to become standard for closed repair of mitral stenosis.

The pioneers of modern surgery of the mitral and aortic valves emerged in the mid 1940's. Horace Smithy of Charleston, South Carolina,[47] had severe calcific aortic stenosis and was a determined investigator of this disease. His own experiments led to a subsequent failure of the first attempted aortic valvotomy at the Johns Hopkins Hospital, and he died soon thereafter of pulmonary edema and left ventricular failure. Meanwhile, three pioneers in cardiac surgery, Charles Bailey of Philadelphia,[1] Dwight Harken of Boston,[32] and Russell Brock of London,[9] reported success in mitral valve procedures, mitral commissurotomy, valvuloplasty, and valvotomy. Subsequently, Bailey,[2] following the lead of Horace Smithy, developed a technique of dilatation of the calcified and stenotic aortic valve. The instrument introduced through the apex of the left ventricle in some instances produced good results but often the results were less than satisfactory. The need for direct vision techniques of cardiac surgery using cardiopulmonary bypass was dramatically revealed by some of these pioneering procedures. Soon they became routine and were the first cardiac operations to be done in large numbers. Pulmonic stenosis was successfully relieved by using a variety of cutting instruments developed by Russell Brock and T. Holmes Sellors,[9, 45] working separately in London. The valvotomy instruments were introduced transventricularly and the results were satisfactory.

The "Open Heart" Era

As the need for operations performed inside of the heart under direct vision became increasingly obvious, the challenge was even greater to those working in experimental laboratories. One method emerged which enjoyed only a brief application, i.e., circulatory arrest during hypothermia. Dr. F. John Lewis, at the University of Minnesota,[35] was perhaps the earliest pioneer in hypothermia for open

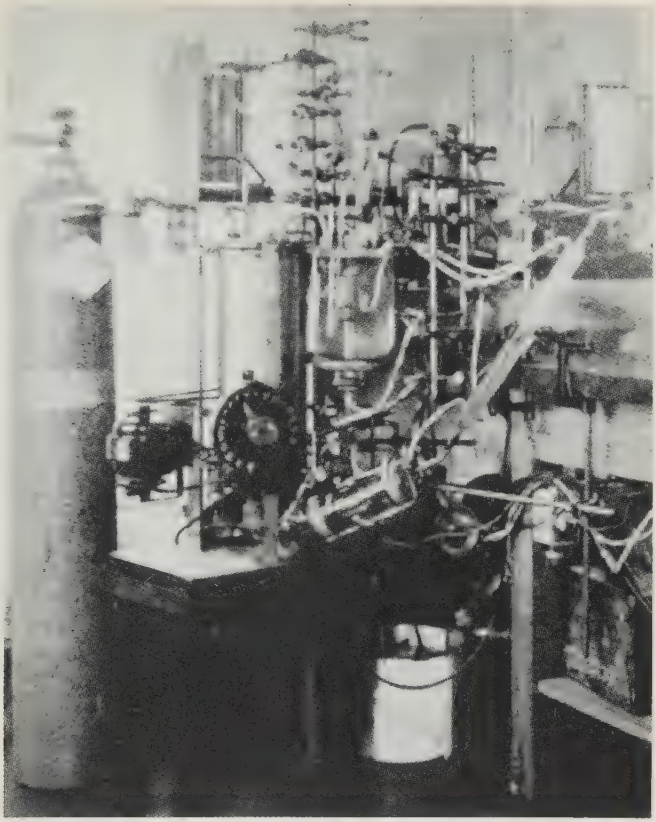

Figure 1. Equipment used by John Gibbon in early laboratory experiments in extracorporeal circulation. More refined equipment was used in 1953 during the first open heart operation performed by Dr. Gibbon and his staff when they repaired an atrial septal defect.

heart surgery. Among the other investigators in this field, W. G. Bigelow of Toronto,[5] Henry Swan of Denver,[31] and W. H. Muller then in Los Angeles[37] perhaps contributed the most. Unfortunately, the time allotted for intracardiac surgery by this technique was extremely limited with an upper limit of approximately 10 minutes. Therefore, the operations were frequently done in haste, and incomplete closure of relatively simple defects often resulted. The more complicated defects such as atrioventricular canal and large ventricular septal defects could not be repaired by this technique. It became increasingly obvious that more dependable methods were needed. Dr. John Gibbon of Philadelphia[25] and Jefferson College of Medicine had been working in his laboratories for more than a decade on a device that would provide for oxygenation and circulation of blood in an extracorporeal circuit (Fig. 1). Finally, in 1953, a test of his open heart technique with total cardiopulmonary bypass was utilized in a patient with an atrial septal defect. The success of that operation was a strong stimulus to other investigators.

Much credit belongs to C. Walton Lillehei of the University of Minnesota,[36] who with his team made extracorporeal circulation and cardiopulmonary bypass a clinically safe technique (Fig. 2). Their first clinical application of artificial circulation was with cross circulation—a technique that had been used experimentally for many years in laboratory investigations. To obtain open heart conditions in a small child, they would enlist the blood compatible mother or father as a donor to provide for oxygenation of blood. The pump in the cross circulation circuit was used to control the volumes of blood passed in and out of the recipient (Fig. 3). The remarkable aspect about those early operations was that among some 40 patients who were

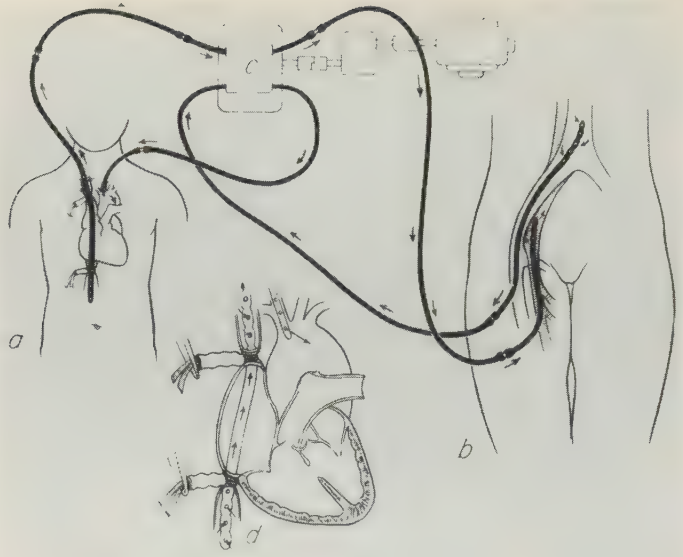

Figure 2. Cross circulation between patient and parent, as used by C. Walton Lillehei and associates, was the first consistently successful open heart surgery using temporary extracorporeal circulation. Although clinical results were good, the threat to the donor, along with other problems, caused this method to be discarded when mechanical oxygenators became available for clinical use.

operated upon for septal defects and other intracardiac lesions, the surgical mortality was about 5 per cent. Fortunately, only one donor suffered serious complications and that was a mother who sustained a cerebral embolism, probably due to entrapment of air.

From this beginning, Lillehei and his associates realized that open heart surgery with temporary cardiopulmonary bypass was feasible. While many members of Lillehei's group were studying different types of oxygenators, the one devised by Richard DeWall[19] proved to be the most practical. This was a simple bubble diffusion system with a helical coil for defoaming the blood, using a silicone antifoam substance. With this mechanical oxygenator and a pump in the circuit, open heart surgery finally became a practical reality. Many more complicated defects such as tetralogy of Fallot, ventricular and atrial septal defects, and other lesions became amenable to surgical correction. John Kirklin[34] at the Mayo Clinic continued his work with the more complex Gibbon type apparatus and demonstrated that open repair of complicated defects could be accomplished with low risk.

My entry into the field of open heart surgery using temporary cardiopulmonary bypass was in 1955 and 1956. We modified the DeWall oxygenator and built a vertical stainless steel oxygenator based on the same principle as DeWall's, which was easier to assemble and use. With this device incorporated with a roller pump system, my associates and I rapidly gained experience with large numbers of successfully performed open heart operations.

The next major modification came with the development of plastic disposable oxygenators. The original oxygenator devised by Rygg of Copenhagen[42] and a modified model designed by Vincent Gott of Minneapolis[18] soon replaced the permanent reusable type of oxygenators. Early in the experience it was customary to prime the extracorporeal circuit with freshly drawn heparinized blood (Fig. 4). Through the work of Zuhdi, Gadboys and Litwak,[23, 55] and ourselves, it was soon demonstrated that techniques of hemodilution could be applied in using a 5 per cent dextrose solution exclusively to prime the extracorporeal circuit (Fig. 5). These techniques are still in use in our hospital, where bloodless primes have become a standard. The

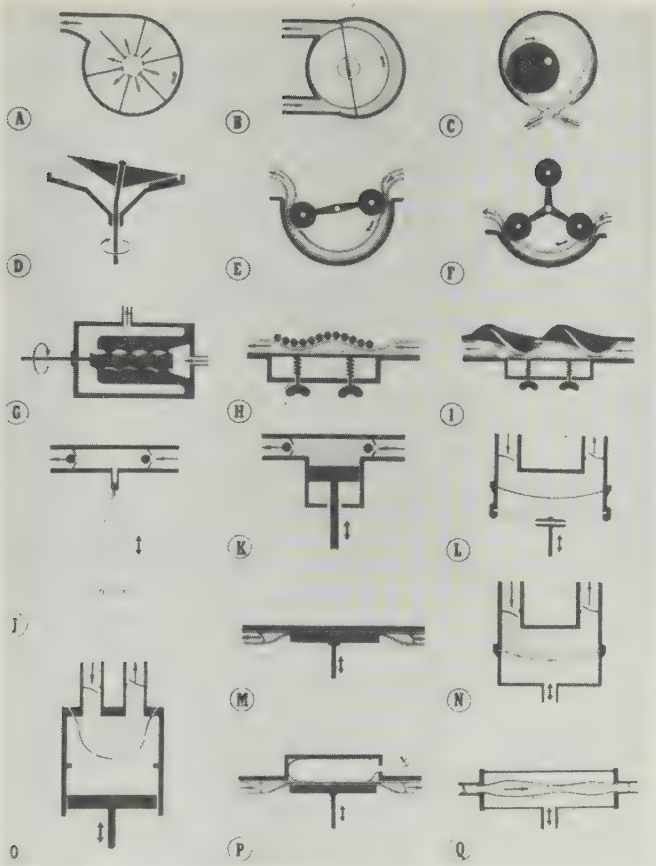

Figure 3. Types of blood pumps available for extracorporeal circulation. (Lillehei used the multiple finger pump shown in B.) Roller pumps E and F have been used for blood handling in transfusions since 1924 (Beck), but similar pumps were patented before 1850. Although the roller pumps have enjoyed the greatest clinical application, recently a centrifugal pump (Biomedicus) that causes minimal blood damage was introduced. (*From* Galletti, P. M., and Brecher, G. A.: Heart-Lung Bypass. New York, Grune and Stratton, 1962, with permission.)

heavy burden placed upon blood procurement units was relieved, and this greatly facilitated application of open heart techniques. The complications of extracorporeal circulation such as pulmonary insufficiency, low output failure, mental confusion, and subsequent hepatitis were greatly reduced.

With this new simplified technique of open heart surgery, surgeons privileged to be involved in cardiac surgery at the time suddenly found themselves in roles of active exploration. It was almost as if a key to a door entering an unexplored wilderness was suddenly found. Those of us who were privileged to pass through made exciting discoveries. The pace of progress quickened, and expanded activities followed.

Acquired valvular heart disease was then amenable to surgical correction. Some of the closed techniques such as mitral valvotomy became feasible under direct vision, with improved results. Aortic and mitral stenosis were lesions that were first attacked by debridement of calcium with salvage of the valve. But in the majority of instances, particularly with the aortic valve, it became obvious that a prosthesis for total valve replacement was necessary. Credit for developing valvar prostheses belonged to many investigators and surgeons of that period. However, to Albert Starr (now of Portland, Oregon) and to Dwight Harken belongs the major

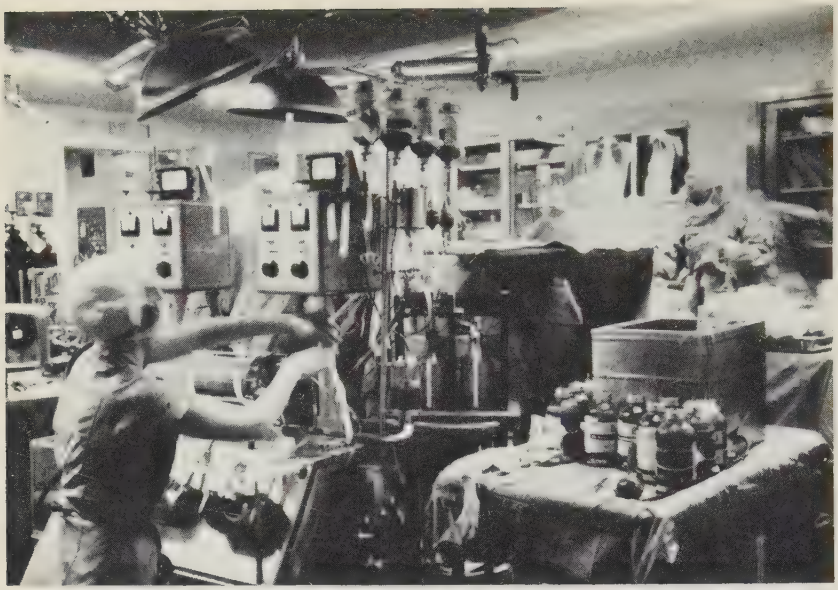

Figure 4. Operating room scene circa 1960 showing cumbersome pump and oxygenator equipment used during that period. Of particular interest are the 14 units of heparinized, freshly drawn blood used to repair a simple atrial septal defect. Adoption of hemodilution techniques with smaller volume extracorporeal circuits made open heart techniques safer and more practical.

credit for bringing valve prostheses to clinical use. Others had labored toward making a prosthesis to imitate the anatomy of the human valve, but Starr[50] utilized an old principle in using a caged ball design. Those early operations were most encouraging and led to great interest in the development of better prostheses. Unfortunately, many of the early models were subject to material deterioration, and during the ensuing 15 years—and until quite recently—degradation of materials has been a serious problem. Materials that seemed completely durable in the testing laboratory soon showed signs of wear and deterioration. More recently, better materials have been available and long-term results have improved.

The major problems with the use of synthetic prostheses, namely thromboembolic complications, have caused many surgeons to adopt biological tissue valves, which are relatively free of such complications. The valves currently in use are either porcine xenografts or homologous pericardium fashioned into the tricuspid configuration. Both types are preserved in a stabilized glutaraldehyde medium. The design of an ideal prosthetic valve made entirely from synthetic materials remains a challenge for the future. The need for anticoagulants as used with most synthetic valves introduces an additional inconvenience and risk to the patient.

Another important advance in modern heart surgery has been the development of pacemakers. Credit belongs to Paul Zoll of Boston[54] for demonstrating the feasibility of implanting an electronic device that would provide the necessary electrical stimulus to pace the heart. Pacemakers have become useful in other syndromes, including tachyarrhythmia and the "sick sinus" syndrome with intermittent periods of brachycardia and cardiac irregularities. Among the remaining problems is the deterioration of electrodes due to electrolysis and the short life of the batteries. One of these problems has been partially solved with the recent introduction of lithium iodine batteries. The future promises both a pacemaker and leads that will be guaranteed for the life of the patient.

Improvement in oxygenator design must continue. Recently, the bubble oxygenator has been replaced in some centers by membrane oxygenators in which a membrane is placed at the blood gas interface. This appears to reduce the amount of trauma to the blood with reduction in postoperative hemorrhagic, renal, and

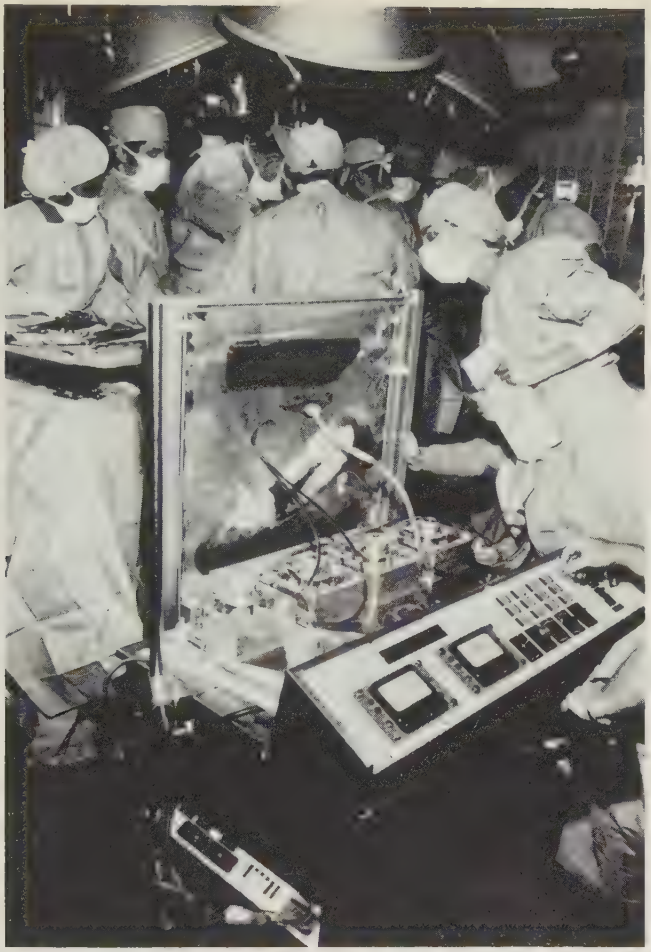

Figure 5. Modern open heart surgery scene showing the use of a plastic disposable bubble diffusion oxygenator primed with dextrose and electrolyte solutions. Simplicity and efficiency of the current techniques have contributed to the safety of extensive cardiac repair.

pulmonary complications. Unfortunately, this principle does not provide the high efficiency characteristic of bubble oxygenators. The pumps used in extracorporeal circulation will be significantly modified in the future. While the standard method has involved the use of a continuous flow system, it appears that pulsatile flow may be advantageous, and several devices are now in use to provide this modality.

A recent wave of renewed interest has centered around preservation of myocardial viability during the period of aortic cross clamping and myocardial ischemia. Depending upon the length of time, the temperature of the myocardium, and other factors, myocardial damage during ischemic arrest may lead to serious sequelae, including myocardial necrosis and later fibrosis. Recently, the use of cold cardioplegic solutions containing potassium ion and other substances has shown promising results and may prevent many such complications.

As the field of cardiac surgery expands, the need for new diagnostic techniques increases. Since arteriosclerotic cardiovascular disease is the major cause of death in this country and in all Western societies, it is important that interest be focused on these diseases. Coronary occlusive disease is the most prevalent cardiac disease today. The development of selective coronary arteriography by Mason Sones in Cleveland,[48] therefore, must be recognized as one of the major advances in cardi-

ology and cardiac surgery. For the first time, surgeons have the ability to identify and delineate the nature and extent of the coronary occlusive disease. With the development of direct techniques of myocardial revascularization using vein bypass grafts, the outlook of patients with manifestations of this disease has strikingly improved. More than double the number of heart operations have been performed in recent years compared to just five years ago. During the current year approximately 100,000 myocardial revascularizations will be performed in the United States. The fact that perhaps several million patients are potential candidates for myocardial revascularization creates a problem of diagnosis and the screening of patients. Noninvasive techniques offer assistance in the screening process and in evaluating the need for more precise diagnoses. Among the major noninvasive techniques in use today are echocardiography and treadmill stress test electrocardiography. Other diagnostic tests gaining interest are those using the various scanning mechanisms with radioisotopes.

Personal History and Observations

After graduating from the University of Texas in 1941, I entered medical school at the University of Texas Medical Branch in Galveston, Texas. Because of some administrative turmoil at the medical school, I decided to transfer for the third and fourth years. I was accepted at Johns Hopkins University Medical School in Baltimore, Maryland, where I joined the junior class in February of 1943, graduating in August, 1944.

My inclination then was to take a rotating internship, and my first choice was at the University of Michigan at Ann Arbor. However, Dr. Alfred Blalock, Professor of Surgery, prevailed upon me to take a straight surgical internship at Hopkins. Fortunate indeed it was for my career that I accepted his invitation, for he was at the time working in the Hunterian Laboratory (we called it the "dog lab") with his fabulous assistant, Mr. Vivien Thomas, on techniques of creating systemic pulmonary anastomoses for the study of pulmonary hypertension. Dr. Helen Taussig had suggested the possibility of creating such a shunt for relief of cyanosis in tetralogy of Fallot. In November, 1944, the first operation was performed. I was the intern on the case and received my first stimulus in heart surgery. Imagine the excitement that followed those first experiences when cyanotic children suddenly became pink as the clamps were released and the anastomoses began to function. Within 12 months I became Dr. Blalock's first assistant on the "heart team," an unusual promotion that was due to the war emergency, which had limited the number of available house officers. After spending eight months with Dr. Blalock as his coordinator of the new Cardiac Service, I was called to active military duty in February of 1946 and spent two years in Linz, Austria, as Chief Surgeon in a station hospital. When I returned to Hopkins in 1948, the cardiac service had become the most active one in the hospital. Perhaps the brightest young star, and now Professor and Chairman of the Department, was my contemporary and friend, Dr. Henry Bahnson, now Professor of Surgery at the University of Pittsburgh. He had accompanied Dr. Blalock to Great Britain and France to demonstrate the blue baby technique in a historic tour which was long remembered. Hank was a tough act to follow, but I soon regained Dr. Blalock's confidence. At Johns Hopkins I completed my training as a general and thoracic surgeon in 1950.

One exciting episode at Hopkins was to make a deep impression upon me and strongly influence my development as a cardiovascular surgeon. An emergency arose involving a patient under the care of Dr. Grant Ward, who was best known for tumor surgery of the head and neck. Dr. Ward had previously undergone an operation for a spinal cord lesion and his right arm was in a brace fixed in the abducted, airplane position. The patient previously had had his sternum removed for a chondrosarcoma, and a Vitallium prosthesis had been inserted. The prosthesis had eroded the ascending aorta and the patient had sustained a massive, nearly exsanguinating hemorrhage. This occurred on a Saturday afternoon. He was brought to the operating room where Dr. Ward and I quickly controlled the bleeding, but Dr. Ward had to place his left forefinger in the aortic orifice. With Dr. Ward unable to proceed, it fell my lot to complete the procedure. We successfully repaired the aneurysm of the ascending aorta by oversewing the defect. From that moment, I was convinced that excision of thoracic aneurysms was a definite possibility. Subsequently, I resected a large fusiform aneurysm of the innominate and right

subclavian artery at Hopkins; the case was reported in a paper presented before the Southern Surgical Association in December, 1951.

While I was at Hopkins, Mr. Russell Brock, Britain's foremost cardiac surgeon, spent a month with us as Visiting Professor. I was inspired by his personality and his ability as a surgeon and asked him to let me serve a registrarship on his service in London. When I finished the service at Johns Hopkins in July, 1950, I took my wife and infant daughter, Mary, to London for a year as Senior Surgical Registrar at the Brompton Hospital. The knowledge that I gained there has been invaluable, since Brock was doing many mitral and pulmonic valvotomies and direct surgical attacks on the infundibular stenosis in tetralogy of Fallot. My associations there with the men involved in the emerging specialty of cardiac surgery, and the friendships gained, have lasted throughout my career.

On returning home to Houston in 1951, I was given an appointment as Instructor in Surgery at Baylor University College of Medicine under the chairmanship of Dr. Michael E. DeBakey. Together we advanced the technique of excisional therapy of aneurysms of the aorta.[16] My interest in cardiac surgery continued, and with the limited training and experience of surgeons in this field, I was able to advance the development of heart surgery in the Texas Medical Center. My identity since then has been mostly as a cardiac surgeon, but also with an extensive experience in vascular surgery.

My contributions to cardiac surgery are modest compared to some of the giants in the field. I introduced techniques for repair of total anomalous pulmonary venous return, repair of postinfarction ventricular septal defect, excision of left ventricular aneurysms, embolectomy for massive pulmonary embolism, reconstruction of the coronary system in congenital coronary anomalies, a method of anastomosis of the ascending aorta and right pulmonary artery for pulmonary ischemia, and other technical procedures for congenital and acquired heart disease. My colleagues and I participated early in the use of bloodless prime for the extracorporeal system with 5 per cent dextrose and water which simplified open heart surgery. Also, I have helped design several artificial heart valves which have been used clinically, and at present, very satisfactory mitral and aortic valve prostheses, known as Cooley-Cutter valves. More than 3000 have been implanted.

Perhaps the most exciting event in the modern era of cardiac surgery came in December, 1967, when cardiac transplantation was performed in Capetown, South Africa. Dr. Christiaan Barnard captured the imagination not only of the medical profession but the world at large, with his temporarily successful transplant on a man named Washkanski.[3] Actually, Norman Shumway of Palo Alto, California, and his colleague, Richard Lower of Richmond, Virginia,[46] had been working experimentally with this technique and were on the verge of performing the same procedure themselves; they were ready and waiting for the opportunity. Barnard's élan and flair raised him to a pinnacle such as few matinee idols have attained.

In January, 1968, Shumway performed cardiac transplants in Palo Alto with limited success at first.[46]

Our own entry into the field of cardiac transplantation began in May, 1968, when we had our first successful transplant. It was probably the first successful case in the United States. The patient, Edward Thomas, survived the operation and was rehabilitated only to die from organ rejection less than a year later. Four months after that first case, we had done cardiac transplantations in nine patients, seven of whom were alive and thriving. We were enthusiastic then, but later the attrition was depressing and our longest survivor was just over one year. In retrospect there are many modifications of technique that I would make today if we had the opportunity. Dr. Shumway's group has persisted in this endeavor and recently reported 109 patients who had received 114 heart transplants since 1968. Five patients have received a second graft. The overall one-year survival was 52 per cent, and recent results indicated a one-year survival of 66 per cent. Forty-four patients were alive at the time of their most recent report. The longest survivor of cardiac transplantation in this country was more than eight years. This record confirms the fact that cardiac transplantation should be considered an acceptable operation for patients who are terminally ill from irreversible heart disease. Perhaps we will have the opportunity to return to this technique in the future.

The alternative to cardiac transplantation lies in the use of mechanical devices for circulatory support. In May, 1969, with my associate Dr. Domingo Liotta, I

performed a two-stage cardiac transplantation in a patient with advanced and terminal heart disease.[12] The patient first underwent open repair of a diffuse left ventricular fibrosis with severe coronary insufficiency. He could not be weaned from cardiopulmonary bypass so we proceeded with orthotopic implantation of a mechanical heart. The device supported his circulation very well and 64 hours later the artificial heart was replaced with a cardiac allograft. Unfortunately, the patient died 36 hours after that from a Pseudomonas infection of the lung. This demonstrated clearly, however, that circulation could be supplied in man by a mechanical device. Further improvement is necessary, and experiments are taking place at this time in the Texas Heart Institute Cardiovascular Research Laboratories under the direction of Dr. Tetsuzo Akutsu. Other institutions in this country and abroad are also performing experiments on the artificial heart. The next attempt at orthotopic cardiac transplantation should be made following the pattern of the two-stage procedure first performed here in May, 1969.

At present cardiac surgeons are mostly involved with treatment of atherosclerotic heart disease and coronary insufficiency. The technique introduced and promoted by Rene Favaloro[20] and Dudley Johnson[33] of Cleveland and Milwaukee, respectively, have led to a boom in cardiac surgery—a boom of such proportions that it sometimes bewilders and even frightens the planners for medical health care delivery. Some of the earlier contributors to the techniques of myocardial revascularization are perhaps forgotten because of the heavy impact of these more recent investigators. For example, Edward Garrett,[24] then of Houston and now of Memphis, Tennessee, perhaps did the first saphenous vein bypass graft for acquired coronary heart disease; and Cooley and Hallman[29] did the first successful bypasses for congenital cardiac anomalies. Already, surgical repair of the serious consequences of myocardial infarction have become more or less standardized. For example, ventricular aneurysms, acquired ventricular septal defects, mitral regurgitation due to papillary ischemia and rupture, and other such lesions are treated almost routinely. With the steady pace of change and improvement in cardiac surgery, the future of this specialty appears secure.

Several problems that face the modern practicing surgeon and physician deserve some mention. For example, health care delivery in this changing specialty challenges the planners at the government level and also organized medicine. The success of the Medicare and Medicaid programs, although not unqualified, indicates that in the future a national health insurance program will be developed. The implementation of such a program with its many implications will cause many social and economic problems. The fact that the public, and particularly the voting public, appears to want this system guarantees that it will become a reality, however unwanted it may be by the medical profession.

One of the major problems that concerns the medical and surgical professions, and particularly those surgical specialists who are working in cardiovascular surgery, is the matter of professional liability and the nuisance of multiple litigations against those of us who are trying to make scientific progress. My own experience with a lawsuit regarding the implantation of the artificial heart in 1969 was an unforgettable initiation for me into the field of medical jurisprudence. In that suit the plaintiff claimed a judgment of $4,500,000. Fortunately, the verdict at the trial was in my favor. Recent suits regarding prosthetic heart valve failures against myself and the manufacturers of valves came to a grand total for four suits of $69,000,000! I was released as a defendant in those cases but plan to help defend the manufacturers to the best of my ability. The recent medical device legislation which brings the Federal Drug Administration strongly into the picture of progress in this field promises to complicate my professional life and efforts to serve my patients. Regrettably, in the future many innovators in the surgical profession, as well as corporations that provide support by introducing new technologies, will be discouraged. Undoubtedly, progress will be seriously curtailed as heavier demands are placed upon each investigational project, however minor it may be. The medical profession is under extremely close scrutiny, and the demand for governmental control will, in my opinion, cause a serious handicap for future investigators.

Many challenges in cardiac surgery remain for the future. For example, surgeons are not yet able to replace all of the components of this marvelous machine, the human heart. Among these components are valves, the cardiac septa, the conduction mechanism, and the great vessels. But what remains is a

substitute for the myocardium. Two efforts must be directed: one toward supporting temporarily the failing left heart, and the other a total and permanent replacement of the hopelessly damaged myocardium. The support devices introduced in the past decade have proved to be moderately effective and show considerable promise for the future. Cardiac transplantation, while it has reached spectacular success in the present era, may gain even greater clinical application in the future, as problems of tissue rejection are solved and methods for organ procurement and preservation are developed. The future of cardiac surgery remains wide open in my opinion; and as we approach the beginning of a new century, the opportunities for young surgeons are even brighter than they were in the middle of the 20th century when cardiac surgery actually had its beginning.

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Wound Healing

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My interest in wound healing developed in the mid-1930's when I was an intern and junior resident under Professor Elliot Cutler at the Peter Bent Brigham Hospital. That was the period when the classic studies of Harvey and Howes had caught the attention and interest of the surgical world. Prior to their work most surgeons thought of Lister and Alexis Carrel as having made the principal contributions to an understanding of wound healing and tissue repair after injury. The principles of asepsis were firmly established, although there were still some surgeons who operated without gloves. Alexis Carrel had shown that slight injury stimulated the healing of wounds. He noted the phenomenon of a "latent period" and together with deNouy developed an empirical formula to predict the rate of healing of a superficial wound. The fundamental and precise observations of John Hunter on war wounds on Bell Isle in 1760 had been largely overlooked. Even today many surgeons are not aware that Hunter accurately described wound contraction, carefully distinguished it from contracture, and demonstrated that the size and shape of a wound influenced the rate of healing. Indeed his observations on wound contraction or intussusceptive growth are still important in the care of open soft tissue wounds in man.

It remained for Sam Harvey and his associates, most notably Edward Howes, to quantify the rate of wound healing by measuring the bursting strength of wounds in the stomach of the dog. They interpreted this as a measure of the rate of fibroplasia which was characterized by a "lag phase" of three to four days preceding a rapid increase in tensile strength followed by a flattening out of the curve at 14 days.[23] On the basis of these studies every medical student was taught that "wounds heal in two weeks," even though Howes shortly thereafter demonstrated that the gain in tensile strength of wounds in the skin continued for many months.[24] Indeed this fact escaped the attention of most practicing surgeons for many years.

Stimulated by the work of Howes and Harvey, a number of papers appeared in the literature. Lanman and Ingalls[31] studied the effects of experimental vitamin C deficiency and the importance of hypoproteinemia and tissue edema was demonstrated by the University of Pennsylvania group headed by Ravdin and Rhoads.[44, 53] Quite independently, Hojer[22] in Scandinavia and Wolbach[54] in America had clearly shown that vitamin C was essential for the formation of mature collagen. This was the general state of knowledge of wound healing when I became involved.

PERSONAL STUDIES

My initial interest in wound healing involved surgical technique and the use of sutures. Our Chief, Elliott Cutler, was a master Halstedian surgeon. He handled

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tissues with extraordinary gentleness but he was by no means a slow operator. I can still hear his admonitions. When he gave an assistant a retractor he would say, "Be gentle, remember it's nothing but water." Whenever an assistant touched the wound unnecessarily, sponged too vigorously, or took too large a bite of tissue with needle or hemostat he would put his hand over the wound, fix the culprit with his cold blue eyes and say, "You have just killed one *hundred thousand* cells!". Most of us, including the great Robert Zollinger learned how to do it properly before we had "killed one *million* cells!"

Although the Brigham Hospital had an excellent senior staff, it was obvious that the Chief's surgical wounds had the lowest incidence of infection and rarely were irritated or swollen. Allen Whipple, Professor of Surgery at Columbia, a recent convert to Halstedian technique, was promoting the use of silk but urging that it should not be used in the presence of infection. Since Dr. Cutler regularly used silk in gastric, biliary, and colonic surgery, it was obvious to me that the moderately contaminated wound was not a contraindication to the use of silk. So together with Dr. Phillip Shambaugh we began some studies in the laboratory to demonstrate this.[48] Simultaneously I reported uniform success in primary closure of pilonidal sinus with silk in contrast to a high failure rate when catgut was used,[10] and later Botsford and I reviewed the experience of the Brigham Hospital with the use of silk in thyroid surgery, showing again a markedly lower incidence of wound complications when silk was used.[11]

In 1941, together with the Chief, I presented a report on postoperative wound infection in contaminated wounds closed with silk.[8] The rate varied from 28 per cent in acute suppurative appendicitis to 7 and 4 per cent in operations on the colon and biliary tract respectively. There were no instances of wound infection following gastric operations. In many of the cases of appendicitis it was obvious that the skin and subcutaneous tissues should have been left open. These results are comparable to many reports in the recent literature with the use of local topical antibiotics, showing once again that surgical technique is the most important factor in the control of wound infections.

During my period in the laboratory 1937–38 as the Arthur Tracey Cabot Fellow, I began studies of the healing of wounds that had been opened and resutured and determined the effect of a distant wound on a fresh primary wound. I was convinced from my observations that a wound that was opened and resutured between the fourth and the sixth day after operation regained tensile strength so rapidly that it was almost as strong as a fresh primary wound that had not been opened at the end of one week. Naively I thought that we might find something in the wound at four days which could be injected to stimulate repair prior to making an incision. At that time Dr. Valey Menkin in the Department of Pathology had found a substance "leukotaxin," which attracted leukocytes into tissues. My idea was to infiltrate the area of the incision with "leukotaxin" 4 to 6 days before making the wound, hoping that the tissues would be in a state of a four-day postoperative wound and that the subsequent incision would heal rapidly. Unfortunately, Dr. Menkin could not provide me with enough material to perform a statistically convincing study.

I did not publish my early observations on the resutured wound because I did not have sufficient data for a statistically sound report. But in 1941 my good friend and close colleague Tom Botsford spent a year in Edinburgh and at my suggestion instituted a series of studies on the healing of the resutured wound. His work was the first demonstration that there are local factors that permit a wound which has been opened and resutured to heal more rapidly than a fresh primary wound.[2]

During this period, the mid-1930's to the early 1940's, there were a large number of important contributions to this field from other workers. Complete credit cannot be given to everyone in this review, but Localio and Hinton[35] made important contributions on tensile strength in relation to suture material. Hilger Jenkins of Chicago also demonstrated the importance of suture material and the irritating qualities of catgut.[29] The most important study at that time, confirming the early work of Howes on the long-term gain in tensile strength, came from Mason of Chicago in a study of healing in tendons.[38] He showed beyond doubt that immobilization through the period of fibroplasia was important, but gentle and progressive use was essential if a tendon was to regain normal tensile strength.

Those interested should read the classic review of Arey in Physiological Reviews in 1936[1] and a review by Localio, Casale and Hinton published in Surgery, Gynecology and Obstetrics in 1943.[36] My own studies of wound healing were tapered off as the war approached when increasing interest was directed to the study of shock at Harvard. I gave up my wound healing studies and concentrated on experimental shock with John Gibson in cooperation with the Harvard Shock Commission. However my role in this project terminated when the Harvard Unit, the 5th General Hospital, was activated in January, 1942.

During the war we were impressed, as were many others, by the slow healing of open wounds in malnourished patients. In Normandy we treated many patients with extensive open wounds and often multiple abdominal fistulae using repeated transfusions of blood and plasma. Although we had no controls, we were convinced that massive amounts of intravenous plasma as well as whole blood hastened the rate of healing. A report was published in the New England Journal of Medicine shortly after the war.[12]

I did not get back to the laboratory to continue studies of wound healing until the late 1940's and early 1950's. Meanwhile, however, Philip Sandblom had published his classic study on the tensile strength of healing wounds in the Acta Chirurgica Scandinavica in 1944.[44] In accuracy, detail, and breadth of coverage this study ranks among the very best and should be read by all interested in this field. Sandblom repeated a number of the classic studies reviewed by Arey on factors that affect repair, but most important of all he described a very accurate method of experimental wound mensuration.

Sandblom observed that there appeared to be accelerated healing of a wound made after a previous remote wound in the experimental animal, thus providing evidence for a "wound hormone." His studies were in accordance with previous work by J. R. Loufborough[37] on a stimulating factor in the healing of plants. Sandblom's observations intrigued me since I had no evidence of a hormonal factor but had found that the resutured wound healed more rapidly than a primary wound, as Tom Botsford had clearly shown in 1941. Accordingly, when I was able to get back to the laboratory and obtain financial support with the help of Dr. Francis Moore I elected to restudy the problem.

The first person to join me as a research fellow was Edward Savlov, now of Rochester, New York. In a long and careful study he showed that under the conditions of our experiments disrupted and resutured wounds rehealed rapidly, but he was unable to demonstrate evidence for a wound hormone.[46] It is of interest that later Phillip Sandblom showed in his experiments that the "wound hormone" effect could be explained by slight trauma to the area of the second wound at the time the first wound was made. Over the years the concept that the disrupted and resutured wound is much stronger than a fresh primary wound has been supported by many investigators including Sandblom, Douglas, and Peacock. Laboratory studies amply confirm the clinical impression that in patients a disrupted wound heals remarkably well, provided there is no infection or nutritional defect. In fact when it becomes necessary to reoperate for complications in the immediate postoperative period, there is a definite advantage in reopening the previous incision. Rapid access is obtained and the resutured wound is almost as strong on the first postoperative day as it would have been if it had not been opened.

I still have the impression that wounds in patients who have repeated multiple operations heal more satisfactorily, and I still suspect that there may be some type of "wound hormone" in mammals such as Loufborough showed in plants. Repeated wounding over a period of many months may be required to demonstrate a systemic wound stimulating factor. If so credit should be given to Loufborough and Sandblom for their original concepts.

A word must be said about the possibilities of having "supernormal healing." Finding a way to accelerate repair has been a dream as old as surgery itself, but the evidence shows that except for the rapid healing of the disrupted and resutured wound, there are no pratical ways to accomplish this. An increase in the rate of fibroplasia has been demonstrated in animals on a high protein diet and after the topical application of many substances including powdered cartilage.[42] However, an increase in fibroplasia in wounds of skin, tendon, and fascia at four or five days

has little effect on the final gain in tensile strength, which is a function of stress and strain and requires many months. Indeed, a considerable increase in tensile strength at five to six days after wounding imparts no more than the pull-out strength provided by nonabsorbable sutures. It is not surprising, therefore, that none of the methods of accelerating repair has been used clinically with the exception of the recent evidence that electrical currents appear to increase the rate of new bone formation in fractures.

Most investigators will agree that chance led to some of their best studies. In my case it was the contributions of Dr. K. N. Udupa from India and later of Dr. David S. Jackson from England.

K. N. Udupa came to the Brigham Hospital to work with me in the early 1950's and we published our first joint study on the chemical and histochemical sequences in the normal healing wound in the New England Journal of Medicine in 1955.[16] Udupa worked in close collaboration with the Department of Biology under Bernard Gould at MIT, and thanks to their cooperation we were able to adapt their studies of collagen synthesis to the healing wound. This initial study, followed by an appraisal of the effects of protein depletion and ascorbic acid deficiency on collagen synthesis, opened up a wide area of research in this field. Udupa has continued his studies in India and presently is Professor of Surgery and Chancellor of Banaras Hindu University. Although we have not seen each other for over 20 years our friendship and association has been continued. I serve on the editorial board of the Indian Quarterly Journal of Surgery of which he is the founder and editor, and many of his pupils have worked in my laboratories in Oregon and California. My associate, T. K. Hunt visited Udupa not long ago as a James IV Traveling Fellow, and at present Dr. Kewal Thakral from Banaras is working with us in the Wound Healing Laboratory at the University of California, San Francisco.

Following Udupa's lead and using a variety of methods for measuring collagen synthesis, we carried out an extensive study of repair at the Boston City Hospital with Louis Pernokas, Dale Flickinger, and Leon Edwards. Edwards proved to be one of the most original, determined, and productive research fellows with whom I have had the privilege of working. He introduced the use of a plastic sponge to sample regenerating tissue in the healing wound and with this method advanced our understanding of the role of vitamin C in fibroplasia. He also produced convincing evidence that the wound fibroblast is of local tissue origin rather than a circulating monocyte which becomes a fibroblast. The status of our knowledge of wound healing in 1958 was presented by us in two review articles in the New England Journal of Medicine.[17]

It was at about this time that Professor J. H. Kellgren, working in the Rheumatology Institute at the University of Manchester, noted the similarity of our observations on wound healing to studies that his group had made in relation to collagen synthesis and its possible influence on joint function. Kellgren and I had met during World War II, so it was a great pleasure for me not only to exchange ideas with him, but to visit his laboratory in the Rheumatology Institute at the University of Manchester where for the first time I met Dr. David S. Jackson, one of the research fellows. This chance meeting eventually led to Dr. Jackson joining us, first as a research fellow, then as an associate in research, and finally as an assistant professor at Harvard. Much of my own knowledge and many of our approaches to studies in wound healing were directed and stimulated by David Jackson. In fact, he provided me with a very sound "cultural" knowledge of collagen chemistry which stood me in good stead in the presence of surgeons. And if I did not talk too much it would even get me by in the presence of biochemists!

During what I shall call the "Jackson Period," we studied the effect of a variety of factors on collagen production including hormones, total body irradiation, bacterial endotoxins, and the effects of stress and strain. Peter Bentley from England, who had joined us as a research fellow, carried out an extensive study of the role of polysaccharides in the healing wound. He subsequently was awarded a Ph.D. in biochemistry from the University of Oregon for this work.

During this same period, Mr. Kevin Cronin from England[6, 7] investigated healing in the colon. We found that a significant loss of collagen from the colon occurred adjacent to the suture line and especially distal to it. The colonic wound rapidly gained tensile strength but the adjacent normal colon became more vulnerable to perforation. These studies were continued later at the University of California.

At the same time Jackson was working on the biochemical sequences in collagen formation. In 1962 we reported some of the practical clinical applications of basic research on wound healing.[14] Much of our work from the Harvard Service of the Boston City Hospital and the University of Oregon was presented in a Moynihan Lecture of The Royal College of Surgeons of England[13] and a Shattuck Lecture of The Massachusetts Medical Society.[15]

During the transition period from Oregon to California, serendipity led F. O. Belzer, J. McK. Watts, and Harvey Ross to the finding that wounds of the common duct can heal by contraction without scarring. They were studying the function of the duct after nearly total excision of the anterior wall with reconstruction by a patch of vein graft. They found that the remaining posterior strip of common duct completely regenerated to replace the vein graft. This was obviously a classic example of wound contraction or intussusceptive growth. Thinking it to be an original observation, we reported it before the American Surgical Association in 1965,[30] only to find later that the same observation was first made in 1913 and the technique was used in a patient by E. Starr Judd of the Mayo Clinic in 1924. "There is nothing new under the sun!"

When I left Oregon close collaboration with Dr. Jackson ended but his influence has been felt in much of our work since then and he has been a frequent visitor to our department. In 1965 he accepted the Chair of Clinical Biochemistry at the University of Manchester, England. It is a source of great satisfaction for a Professor of Surgery to have his residents or research fellows become distinguished academic surgeons, but to have one of the team who joined as a research fellow become the chairman of a distinguished Department of Biochemistry is especially rewarding. The secret, of course, lies not in what the biochemist learns from the surgeon, but in making certain that the biochemical research fellow holds an appointment to teach and participate in all of the activities of the Department of Biochemistry. He should have his space in the Department of Surgery, but his intellectual associations must also have a firm, solid, and welcome place in biochemistry. This requires excellent rapport between the respective chairmen. By adhering to this practice in the appointment of research fellows with a primary interest in the basic sciences, we have had the rewarding experience of having a number of them receive professorial appointments. In addition to Dr. Jackson, there are Peter Bentley, Professor of Biochemistry at Oregon; Ted Cleary, Professor of Pathology at Adelaide, Australia; Milos Chvapil, Professor of Biochemistry at the University of Arizona; Paul Erlich, Assistant Professor of Pathology at Harvard; and Dove Michaeli, Associate Professor of Biochemistry at the University of California, San Francisco.

Meanwhile I had arranged for Thomas K. Hunt, when he finished the Chief Residency at Oregon, to work with Professor Sir Charles Illingworth in Glasgow on the experimental use of hyperbaric oxygen. While there Hunt not only studied the effects of hyperbaric oxygen, but noted that hyperbaric oxygen had different effects when delivered in various concentrations. This led to his appreciation of the role of molecular oxygen in wound healing, and initiated his long-term and exceptionally productive work in this area.

The move to San Francisco was a bit worrisome because Hunt, who already had an excellent handle on basic research, was in Glasgow and we had lost the important guidance and direction of Jackson. Also Peter Bentley elected to stay with Jackson rather than come to San Francisco. Consequently, in addition to reorganizing the Department of Surgery, I had to give far more personal attention to the Wound Healing Laboratory than I had been doing. Happily at this time, Dr. Lokendra Singh came to work with us from Professor Udupa in Varanasi, India. Dr. Singh was a careful, precise, and tireless research fellow. He studied the mobilization of calcium in fractured bones in rats, which, for an extensive analysis of basic factors, will probably never be duplicated.[48]

Initially we were working in limited quarters, but subsequently obtained ideal space for the laboratory in the new Health Science Research Building. By the time Hunt had returned from Glasgow, we had obtained substantial financial support and the stage was set for his broad and basic studies beginning with an analysis of respiratory gas tensions and pH in healing wounds. No sooner was the laboratory under way than we attracted a succession of outstanding research fellows from other countries: J. C. Forrester from Professor Sir Donald Douglas' department

in Dundee; B. H. Zederfeldt from Professor Lars-Erik Gelin's department in Gothenborg, Sweden; Bruce Conolly from the University of Sydney, Australia; J. Niinikoski from Finland; and Peter Hawley from St. Mark's Hospital in London. Also at this time, a college student Paul Erlich, interested in wound healing research and headed for a Ph.D. degree, joined our department to work with Hunt.

Throughout the 1970's there was a gradual transfer of the direction of the Wound Healing Laboratory from me to Hunt, and in recent years all of the research grant support has been in his name. Space does not permit a detailed elaboration of the great breadth and variety of studies which Hunt, together with Dr. Ernest Jawetz, Chairman of Microbiology, and a group of outstanding research fellows have performed. Using a variety of approaches, they have shown that many systemic factors affect oxygen tension in the healing wound, delay repair, and increase the vulnerability of the wound to infection.[27] From the point of view of the clinical surgeon, hypovolemia and shock are of the greatest importance. Mr. Peter Hawley and Drs. Theodore Schrock and Clifford Deveney have presented unequivocal experimental and clinical evidence that hypovolemia predisposes to leakage of colonic anastomoses.[21, 48] In fact, so detrimental are hypovolemia and low flow to healing that they should be considered as possible factors in all cases of postoperative wound infection or dehiscence.

Starting with ideas of our research fellow Paul Erlich, an inhibitory effect of cortisone on wound healing was shown to be reversed by vitamin A.[26] Peter Hawley showed there was increased collagenase activity in the gastrointestinal tract which played a significant role in the rapid degradation of collagen following wounds in the colon.[19] Conolly and Zederfeldt, together with Treat Cafferata, one of our residents, compared wounds closed by suture versus adhesive tapes[5] and found fewer wound infections in the moderately contaminated wounds closed by surgical tapes. James Forrester examined how the physical state of collagen fibers evolves in healing wounds and scars, using the scanning electron microscope.

Other research fellows in the wound healing laboratory who merit mention because of their contributions include Chris Heughan, R. Heppenstall, and Fred Littooy, all of whom worked on various aspects of the role of oxygen in repair.

Professor F. O. Stevens, who worked with us in Oregon, also spent time in the Wound Healing Laboratory at the University of California during a sabbatical period from the University of Sydney. He contributed important additional analyses of the effects of cortisone and vitamin A, as well as the effect of wound dressings on tensile strength of closed wounds.[51, 52] Peter Hawley and later Tom Irwin working with Hunt extended and clarified our earlier studies on collagen formation and wound healing in the colon. It is of interest that studies in progress in Zederfeldt's laboratory at the University of Lund indicate that a colonic wound affects collagen synthesis through the colon.[54]

The abundant evidence of the uniqueness of healing in the gastrointestinal tract as compared with other tissues has been summarized recently by Clifford Deveney and myself.[9]

CONTRIBUTIONS OF OTHER INVESTIGATORS

It is impossible to give adequate credit or even acknowledge all the investigators, particularly those doing basic research, who have contributed to our own areas of interest. The proceedings of a number of meetings held between 1956 and 1970 will provide the interested reader with much valuable factual information and also serve to put in critical perspective the contributions of so many investigators in wound healing or closely related areas.

In 1956 Paul Weiss of the Rockefeller Institute for Medical Research arranged a symposium on wound healing and tissue repair as one of the developmental biology conferences held under the auspices of the National Academy of Sciences, National Research Council. Under the chairmanship of Francis D. Moore, a number of distinguished investigators contributed. Paul Weiss summarized his classic observations on cell movement, migration, stoppage, and remodeling with particular emphasis on the phenomenon of contact inhibition as a factor in controlling growth. The cellular components of repair and methods of analyzing them

were succinctly presented by G. H. Algire of the National Cancer Institute. Karl Myer reviewed the nature and role of the ground substance and a variety of systemic factors affecting repair were described by F. D. Moore, P. J. Gaillard from Leiden, and Stanley Levenson. The nature of healing in bone was presented by Marshall Urist. The proceedings were published under the editorship of W. B. Patterson.[40]

A number of these same investigators gathered together for a three day workshop under the auspices of the National Academy of Science and the National Research Council in December 1963. The proceedings were published in 1966 under the editorship of Stanley Levenson.[32] For number of investigators and breadth of interest in wound healing and related phenomena, this was a most informative and profitable conference. Even today, the data are of practical as well as theoretical interest. Russell Ross of Seattle introduced the meeting with a presentation of the cytology of the fibroblast based on electron microscopic and autoradiographic studies. Collagen biosynthesis was discussed by D. S. Jackson, Bernard Gould of MIT, George Palade of the Rockefeller Institute, Alexander Rich of MIT, and Jerry Gross from the Massachusetts General. A great variety of related factors were reviewed by such distinguished investigators as H. R. Catchpole, Harry Eagle, Paul Weiss, Asboe-Hansen, and Bengt Zederfeldt. Many surgeons, biochemists, and molecular biologists participated.

Three years later a symposium honoring Joseph Lister was held in Glasgow under the chairmanship of Sir Charles Illingworth.[28] All aspects of the healing process were presented by a distinguished group of British and European investigators including Lord Flory, Sir Ashley Miles, W. S. Bullough, W. G. Spector, and Michael Abercrombie. Mary Barber of the Postgraduate Medical School, London, discussed the problems of wound infection and drug resistance. The dangers of the indiscriminate use of antibiotics were stressed and the theoretical advantage of accepting infections of low virulence rather than wiping out these organisms with antibiotics and creating more virulent antibiotic resistant strains was postulated. In summarizing certain aspects of the meeting, I was lead to point out that, inappropriate as it might seem at a Lister symposium, we might find that a certain amount of nonvirulent bacteria were desirable in the wound! It is of interest, therefore, that recently Enquist[42] and his colleagues have found that a certain degree of bacterial contamination appears to stimulate repair. As I suggested at the Lister symposium, organisms are good for the garden and perhaps a few may be good for the wound!

Two years later a centennial symposium on Repair and Regeneration was held under the auspices of the Department of Surgery at the University of California Medical Center, San Francisco.[17] Particular emphasis was placed on the biological aspects of repair and collagen biosynthesis with up-to-date presentations by most of the leaders in the field, including Paul Bornstein, W. S. Bullough, C. G. Cochran, Clifford Grobstein, W. G. Spector, and B. W. Zweifach. The traditional "wound healers" from the United States, Scandinavia, and the United Kingdom once again renewed their association, exchanged ideas, and profited from the depth of the presentations by the basic scientists.

It was now becoming evident that collagen, like other proteins, is synthesized on polyribosomes, but a unique additional step, the hydroxylation of proline and lysine, is required before a normal fibril can be produced. For the hydroxylation of proline, a-ketoglutamate, ascorbic acid, iron, and molecular oxygen are required. The need for oxygen highlighted the importance of Dr. Hunt's studies on factors affecting tissue oxygen tension.

Several important reviews and monographs on wound healing merit mention. Reference has already been made to Arey's review in 1936. An extremely valuable monograph on regeneration and wound healing by A. E. Needham was published in 1952. It has been for me a sort of "old testament" reference for ideas as well as information. Needham's analysis of remodeling as part of regeneration outlines the basic factors in wound contraction first described as noted earlier by John Hunter. John Schilling summarized much of the progress made between 1936 and 1968[48] and a classic monograph "Surgery and Biology of Wound Repair," by Erle Peacock and Walton VanWinkle published in 1970, remains an important reference work.

Particular mention must be made of the role of Walton VanWinkle, Jr., who has been an "intellectual enzyme" in this field. As the Director of Medical Research at Ethicon, he regularly convened the leading surgeons and investigators in this field and since his retirement from Ethicon, and joining the faculty at the University of Arizona, Tucson, he has continued his interest and has published several classic reviews of various aspects of the reparative process.

No single study group can encompass all the aspects of repair. Thus, we have studied wound contraction in a limited way in our department, and so our thinking has been greatly influenced by the observations over the years of Michael Abercrombie, Rupert Billingham, D. W. James, Jerry Gross, H. Grillo, Guido Magno, and H. A. S. Van den Brenk. Epithelization and mesenchymal epithelial interactions have not been a major project for our group and we have based our concepts and writings on the extensive studies of W. S. Bullough, Philip Grobstein, Theodore Gillman, and R. M. McMinn. Although we studied the factors affecting tensile strength the contributions of Professor Sir Donald Douglas, Stanley Levenson, and Philip Sandblom have contributed greatly to our concepts. Finally, Hunt would be the first to acknowledge the basic contributions of Professor Ian Silver of the University of Bristol, England, to our work on oxygen tension in the healing wound.

Special mention should be made of the imaginative studies of Erle Peacock and his colleagues on methods of modifying scar formation. The use of BAPN to produce a pharmacologic state resembling lathyrism in the experimental animal has shown that the formation of scar tissue can be prevented. Although this has not as yet led to the practical use of specific agents that might prevent intraperitoneal adhesions or scar tissue around tendons in man, Peacock's studies point the way for future work.

Studies of wound healing in man have been largely restricted to an evaluation of the effects of surgical technique and the use of sutures on wound complications or wound dehiscence. However, two classic studies, one by S. W. Hartwell and the other by Philip Sandblom, on the healing of wounds in man are strongly recommended.[19, 34]

The current work in the Wound Healing Laboratory at the University of California, San Francisco, is entering a new and exciting phase. David Hohn, collaborating with Hunt, is opening up a new field in the exploration of factors that stimulate repair as well as those that prevent or accelerate infection. Hohn and Hunt have shown that low oxygen tension interferes with the antibacterial properties of leukocytes. Consequently since the healing wound is characterized by a low PO_2, the leukocyte is rendered comparatively ineffective. It also appears that monocytes are the initiating factor in fibroplasia and vascularization.

Some years ago I suggested an ideal inflammatory stimulus released a specific substance that initiated rapid healing. To quote, "although the primary precise stimulus is not known the best way to make an ideal fibroblastic response is a clean sweep of the cold knife. Any other stimulus is undesirable. Trauma from repeated needless wiping of the wound, excessive use of ligatures, strangulation of tissues by sutures, exposure to the lint of operating room air and vigorous squirting into the wound of normal saline all contribute to an excessive inflammatory response."[14] The specific factor may be produced by monocytes, but its effective function in the wound depends upon the surgeon himself. There is no substitute for proper surgical technique.

Finally a comprehensive and up-to-date account of the present state of our knowledge can be found in a series of small monographs on the Fundamentals of Wound Management in Surgery, edited by T. K. Hunt and J. E. Dunphy, the first three of which have appeared.[4, 25, 33]

For the benefit of future investigators, I repeat some advice given to me by Dr. John Homans of Harvard in 1939, "Every young man who hopes to be a professor should study either shock or wound healing because there will always be challenges and questions and each generation will require new and better answers."

"There is nothing new under the sun" and Carrels' observation that a little trauma seems to stimulate repair; my own search for a stimulating factor in the wound in the 1930's; the recent observations of Irving Enquist that a little bacteria present in the wound stimulates repair; and Tom Hunt's elucidation of the role of oxygen constitute a continuum of ideas leading to the cells themselves.

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Gallbladder Disease

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Historical Aspects

Historians loosely refer to cholecystostomies as having been performed two or three centuries ago. However, these early procedures refer to ruptures of the gallbladder through the abdominal wall, and extraction of stones from within the abscess cavity by the physician. Actually the first real operation was a cholecystotomy performed by John Bobbs of Indianapolis June 6, 1867. Surgeons rapidly discovered that cholecystostomies were safer than cholecystotomies, and numerous surgeons particularly in England, the United States, and Germany reported many successful operations of the former type. As is true with nearly all operations in the early stages, the mortality rate from both operations mentioned above was quite high. However, Lawson Tait of England reported 14 cholecystostomies between 1879 and 1885, with only one death—remarkably good for that period.

The first cholecystectomy was performed July 15, 1882, by Carl Langenbuch. Correctly, and adhering to modern procedures, he practiced on dogs and cadavers before performing it on any of his patients. Cholecystostomy soon gave way to cholecystectomy because surgeons realized that the former procedure was often followed by complicating features including reformation of stones.

It is remarkable how much progress was made in the development of surgery in the next few decades. It can be appreciated by perusal of a book on "gallstones" published by Moynihan[15] in 1905; it has a modern touch to it, even to the extent of illustrations (Fig. 1).

During the nineteenth century and the first two decades of the twentieth, progress in surgery was based on anatomical aspects. However from the latter period on, progress was based primarily on physiological and biochemical aspects. Examples are innumerable, but only one will be listed. Walters[18] reported (1921) that at the Mayo Clinic, of 29 patients with jaundice who died after operation on the gallbladder, 16 died of postoperative hemorrhage, whereas of 34 patients without jaundice who died postoperatively, only two of the deaths were due to hemorrhage. This indicated clearly that in many patients the jaundice was a factor in producing the hemorrhage. The high incidence of fatal hemorrhage in the presence of jaundice was noted by all surgeons at that time. It accounted for many deaths, only a minority of which were associated with an operation. The cause was a bit complicated, perhaps explaining why several years were required to solve it. Due to the research work of Dam, Quick and others, it was found that even though the bleeding and clotting time is usually normal, the clot is defective because of a diminution in the conversion of fibrinogen to fibrin. This is an indirect result of the prothrombin deficiency which in turn is due to a lack of vitamin K. Administration of vitamin K–like substances prevents this hemorrhage.

Diagnosis

When the manifestations are typical, a diagnosis of acute or chronic cholecystitis can be made readily and with certainty. However, in many cases the manifestations are sufficiently abnormal to make diagnosis difficult.

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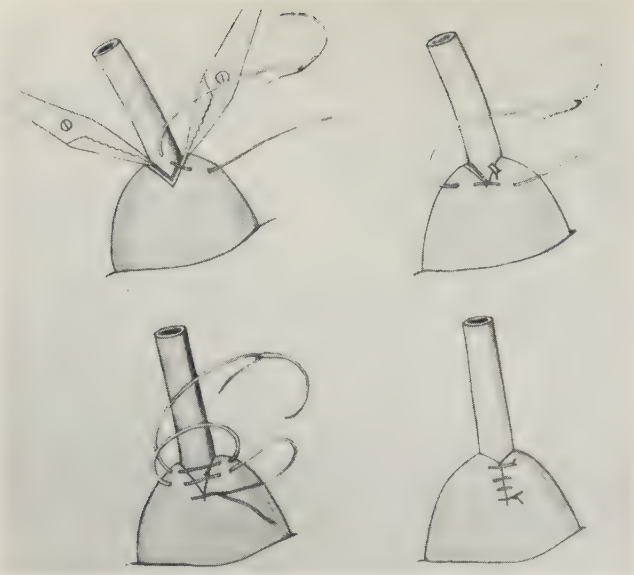

Figure 1. The gallbladder has been opened and its contents extracted, after which a rubber tube is inserted and held in place by a suture "enfolding the edges of the wound into the gallbladder." This illustration is 72 years old and could pass as a modern one. (*From* Moynihan, B. G. A.: Gallstones and Their Surgical Treatment. Philadelphia, W. B. Saunders Company, 1905.)

Dyspepsia is perhaps the most common symptom encountered in chronic cholecystitis. Dyspepsia is difficult to define but may include such complaints as bloating, epigastric distress, pyrosis (heart burn), flatulence, anorexia, belching, and mild pain. Actually dyspepsia is encountered in so many other diseases that its presence is of very little diagnostic aid. The same may be said of sensitivity to fatty foods, although it may be of slightly more aid than dyspepsia.

The *type of pain* is of great value. In the majority of cases it is located in the right upper quadrant, often radiating to the tip of the scapula. It varies in intensity from a mild degree to the most severe pain inflicted upon man. Contrary to the conceptions of the average physician, pain is rarely continuous. In a study of a large number of cases, Harridge and Helsby[12] noted that the attack of pain lasted less than one hour in 40 per cent of patients; also, only 45.6 per cent had pain only in the right upper quadrant. After an extensive study of a large number of patients at the Mayo Clinic, Smith[17] noted that 24 per cent of patients with gallbladder disease had pain left of the mid line, although many of these also had pain on the right. One of the most important features of pain is the fact that if the pain is continuous for more than several hours, one can almost always eliminate the diagnosis of chronic cholecystitis unless a hydrops or empyema exists. In 5 to 10 per cent of patients the history will reveal no pain.

Jaundice often creates diagnostic problems, partly because there are so many causes. After a study of four large reports involving over 1500 patients with jaundice the author noted viral hepatitis was the cause in 18.7 per cent of patients, cirrhosis in 19.3 per cent, cholecystitis and common duct stone in 31 per cent, carcinoma in 23.8 per cent, and miscellaneous in 8.8 per cent. Although stone in the common duct was the cause in less than half of the patients, that diagnosis must always be kept in mind because an erroneous diagnosis without correction can be damaging (even fatal) to the patient.

In the author's opinion liver function tests are not used as much as they should be in the differential diagnosis. With very few exceptions, when the jaundice is caused by stone in the common duct and not accompanied by a prolonged history of high fever, thymol and cephalin tests will be negative, although the alkaline

phosphatase test will be positive. In a report made by Hunter[14] to emphasize the value of liver function tests, he noted the thymol test was positive (over 4 units) in a large percentage of patients with extrahepatic obstruction, but so mildly positive that the average was only 4.3; the cephalin test was positive in only 5 per cent of this group. In viral hepatitis the thymol test was strongly positive in Hunter's series with an average of 15 units (normal up to 4); it was positive in 98 per cent of his 48 patients with hepatitis. The bromsulphalein test is not of much value in jaundice since the bilirubin interferes with the test. One of the tests most helpful in cirrhosis is the albumin globulin ratio which will show a reversal in over half of patients, but will rarely be reversed in the early stages of viral hepatitis and extrahepatic obstruction.

When *stones* are present *in the common duct*, pain will be present in the right upper quadrant or epigastrium in over 80 per cent, more often in the epigastrium than in patients with gallbladder disease alone. Occasionally it is present only at the onset of jaundice; under such circumstances the patient may forget about the pain and give a misleading history. In 35 to 40 per cent of patients there will be a history of chills and fever. A history of jaundice will be present in perhaps 60 per cent of cases, but at operation scarcely more than half will be jaundiced. Usually the jaundice is intermittent. Obviously the treatment of stones in the common duct is operation and removal of the stones.

Development of Cholecystography

In the early 1920's the diagnosis of cholecystitis and gallstones, which were and still are common complaints requiring specific therapy (usually of the operative type), was based almost entirely on history and physical examination. As stated earlier, the manifestations of gallbladder disease are so inconstant and varied that many, many errors were made, sometimes with disastrous results, often resulting in death of the patient. Roentgenologists were aware of the importance of making an accurate diagnosis, and between the years 1915 and 1923 were working on several roentgen methods or observations which might aid in diagnosis. Calcium stones will cast a shadow on a plain x-ray film, but only a very small per cent of gallstones are of this variety. Adhesions caused by pericholecystitis might cause deformity of adjacent intestinal organs, especially the stomach and duodenum; these deformities might be observed by the radiologist during a barium meal and diagnosed as gallbladder disease, but the incidence of error in interpretation was high. A large distended gallbladder might cause an impression

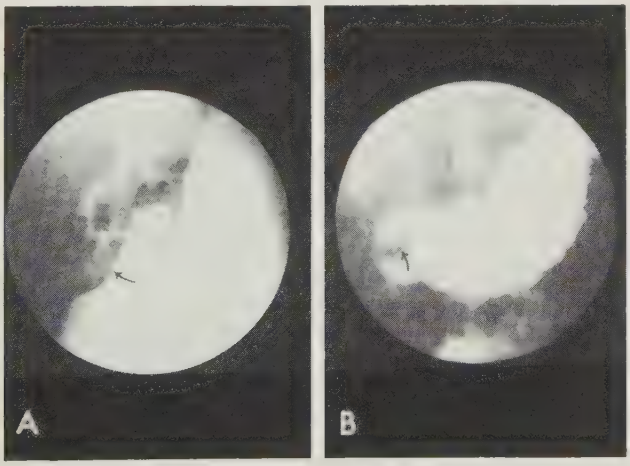

Figure 2. Before cholecystography it was thought that an impression on the stomach (as shown in *A*) indicated the presence of a large diseased gallbladder, but cholecystography reveals a normal gallbladder in *B*. (*From* Graham, E., Cole, W., Copher, G., et al.: Diseases of the Gallbladder and Bile Ducts. Philadelphia, Lea and Febiger, 1928, with permission.)

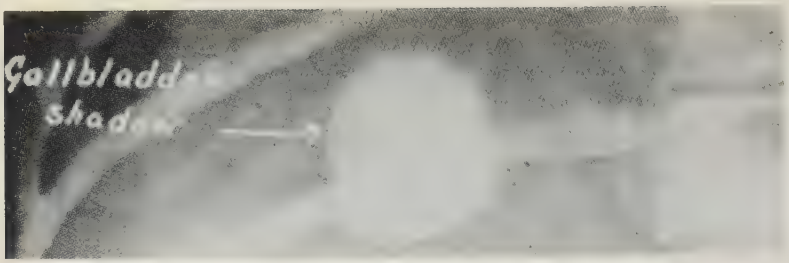

Figure 3. The first successful cholecystogram in a dog. The animal, weighing 5.25 kg, was given 1.5 gm of tetrabromophenolphthalein with 0.3 gm of calcium hydroxide. (*From* Graham, E., and Cole, W.: Roentgenologic examination of the gallbladder. J.A.M.A., 82:613, 1924, with permission.)

on the adjacent stomach demonstrated by barium studies. However errors in this observation were also common (Fig. 2). It was noted that when the gallbladder wall became thickened because of disease, it might cast a shadow on a plain film. Here again errors were common. L. G. Cole, A. W. George, and R. D. Leonard were pioneers in the development of these roentgen tests.

Dr. Evarts A. Graham who was Professor and Head of the Department of Surgery at Washington University, St. Louis, naturally was aware of the importance of correct diagnosis in biliary disease, and the inaccuracy of the roentgen tests used at that time. He conceived of the possibility that the attachment of halogens (especially iodine and bromine) to phenolphthalein compounds might yield a component which would cast a shadow of the gallbladder on a plain x-ray film. He asked me to work with him on this project. This concept would not have been possible without the previous work of two groups of research workers.

In 1909 Abel and Rowntree,[1] who were working on intravenous cathartics, reported that about 90 per cent of phenoltetrachlorophthalein administered to dogs hypodermically was excreted by the liver, and although colorless as the conjugated and free forms, could be demonstrated (by a red color) by adding a drop or two of alkali to bile collected a few hours after administration of the material. They found that phenolphthalein itself was excreted primarily by the kidneys. The other experiment was that reported by Rous and McMaster,[16] showing that the normal gallbladder was able to concentrate 8 to 10 times by absorbing water.

Dr. Graham was busy with academic duties, in fact so busy that I saw him very infrequently. So most of the planning of the experiments was up to me. Very few of the bromine and iodine compounds of phenolphthalein which we wanted to try were available, so we obtained the aid of Mallinckrodt Chemical Company to make them for us. The first compound we tried was tetraiodophenolphthalein. We were fortunate in this respect because our chemist found some of this compound on a shelf in his laboratory. It yielded an inconstant toxicity, due no doubt to the age of the compound. Our chemist was able to make a bromine compound which we used for the next several weeks until he could make a new supply of iodine compound.

I had injected 200 or more dogs and rabbits without obtaining a single shadow. Then one day a very dense gallbladder shadow was obtained in one of four dogs (Fig. 3). I went over my log book trying to find some explanation for the one positive and three negative animals but found nothing to explain it. I then called in the animal caretaker, inquiring if he knew of any difference in the animals. He steadfastly denied knowledge of any difference in the animals until I told him the one dog I was inquiring about reacted the way I wanted him to. Thereupon he said, "Well Doc, there was one difference. I forgot to feed that animal the morning you injected him." I had been reading everything I could find on the physiology of the gallbladder and recalled I had read only a few days previously a short paper by the famous physiologist Boyden of the University of Minnesota stating that feeding cats caused the gallbladder to empty. I realized this was probably the explanation for the dense shadow. When I changed the routine to no food the morning of the injection, I obtained good shadows in almost all animals. I must admit serendipity played an important role in the success of the program, because if I had not read the short report of Boyden's on the effect of feeding on the cat's gallbladder, and had I not

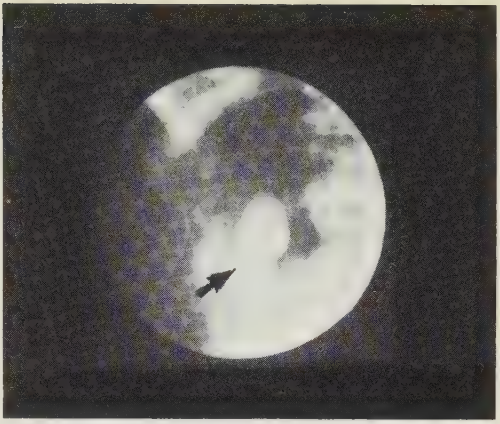

Figure 4. The multiple shadows indicated by the arrow were thought to be gallstones, but the dense gallbladder shadow obtained on cholecystography indicates that they are outside the gallbladder and probably in the kidney. (*From* Graham, E., Cole, W., Copher, G., et al.: Diseases of the Gallbladder and Bile Duct. Philadelphia, Lea and Febiger, 1928, with permission.)

appreciated its significance, someone else would have obtained the first cholecystogram. We found that 13 of 89 drugs tested in animals would produce a shadow of the gallbladder, but sodium tetraiodophenolphthalein was the best for use in humans; it was used for 13 years, at the end of which time priodax was introduced by two Germans.

We wasted no time in trying the method on patients in the hospital, starting out with one-fourth the dose we expected would be necessary in humans. Fortunately the amount of drug necessary to produce a shadow in the human being was less than one-half that necessary in the dog. One or two patients who received an adequate dose had a good history of gallbladder disease, so a negative shadow in those patients meant nothing and we knew it. The first positive shadow in a patient was obtained in a nurse who complained of pain primarily in the back on the right side. The normal dense shadow obtained probably saved her a needless operation on the gallbladder, because her final diagnosis was renal—associated with a nephroptosis and probable ureteral kink. Our initial publication[11] was followed rapidly with numerous reports by workers dealing with use of the iodine compound, the sodium salt, oral method, etc., most of which we were likewise working on simultaneously. The following names represent some of the group who contributed to this phase of the problem: L. R. Whitaker, G. Milliken, T. O. Menees, H. C. Robinson, B. M. Fried, M. B. Sosman, P. J. Edson, and J. T Case. We soon learned that visualization of the normal gallbladder was very helpful in making a diagnosis or in excluding the gallbladder as a possible explanation of the symptoms (Fig. 4).

Numerous features of cholecystography were slow to be ironed out. Some are not understood today. For example, numerous physicians including radiologists order *repeat cholecystogram* is the first one shows no shadow, i.e., indicating a pathological gallbladder. The author contends that with few exceptions (e.g., obese patient, severe liver disease, or substandard film), it is not necessary. However, in view of no shadow, someone must check to be sure the patient took the tablets, did not vomit them, and did not develop diarrhea. The physiology of the patient's liver and gallbladder is so constant that if no shadow of the gallbladder is produced, one can be assured of the test's accuracy, if none of the abnormal circumstances mentioned above exist.

However, a precaution opposite to that mentioned above must be taken in the presence of a shadow of normal density, and typical symptoms of gallbladder disease constituting what is known as the *false-normal oral cholecystogram.* Here is where cholecystography makes its error (2 to 4 per cent). This has been discussed thoroughly elsewhere recently.[4, 8] Whenever a normal shadow is obtained along with typical symptoms the cholecystogram should be repeated, taking films at frequent intervals hoping that the density of the cholecystogram on one or more of the films will be of the right degree to show up a small gallstone. If the stone is in the cystic duct it may be impossible to visualize. Just as often, fibrous bands or abnormal Heisterian valves may obstruct the cystic duct, and explain the symptoms. Less frequently adhesions outside the duct may produce a partial obstruction.

When the physician is convinced the symptoms are typical for gallbladder disease, and the patient is not malingering, operation should be advised in spite of the normal cholecystogram. At operation the gallbladder wall usually appears normal. The gallbladder and cystic duct should be palpated for a stone. Even though no lesion is seen or palpated in the cystic duct (which is the usual cause of the symptoms) it is usually advisable to remove the organ, removing as much of the cystic duct as possible, hoping to find a stone or obstructing bands (usually tranverse) in the cystic duct.

Controversial Points

In spite of the fact that considerable evidence has been presented indicating infection plays an insignificant role in the etiology of cholecystitis, too much emphasis is placed upon infection. In 1927 Denton reported that in 20 patients with empyema of the gallbladder, cultures were positive in only 40 per cent. Microscopic examination of the contents of a gallbladder with empyema usually reveals numerous crystals (cholesterol, bile salt, etc.) and comparatively few bacteria and leukocytes. In 1940 Womack and Bricker noted that exposure of the gallbladder mucosa to bile in a concentration more than twice normal in a dog would produce a chemical inflammation which is indistinguishable from cholecystitis in humans. In 1951 Twiss and associates reported that in 259 patients with cholecystitis subjected to operation, cultures of bile were positive in only 28 per cent of cases. Andrews was one of the first (1935) to call attention to the importance of bile salts in the bile as a possible cause of the chemical cholecystitis mentioned above. In the author's opinion, with a few exceptions the disease starts as a chemical cholecystitis and after a variable period of time infection may become superimposed.

For many years there has been considerable controversy as to whether patients with *acute cholecystitis* should be treated conservatively or by immediate operation. For years Mulholland and others supported the former plan, whereas Glenn and others supported the latter. In the author's opinion there is no categorical answer to the question. Those advising immediate operation do so because of the danger of perforation of the gallbladder, which if free into the peritoneal cavity is apt to be fatal unless operation is performed within a few hours after perforation. The present author contends that each patient with acute cholecystitis must be considered as a separate problem, with treatment depending upon certain factors. If the patient is seen within 48 hours after onset of symptoms and the diagnosis appears quite accurate, prompt operation is advisable. If the diagnosis is doubtful and no significant evidence of peritonitis is present, delay of operation is advisable with performance of diagnostic tests. All surgeons would agree that if signs of peritonitis, with muscle spasm, leukocytosis, vomiting, fever, and persistent or increasing pain are present or develop, prompt operation is advisable because of the danger of perforation.

The treatment of the *silent stone* has been, and still is, the source of considerable controversy. Some physicians contend that as long as no symptoms are produced, there is no need for its removal by cholecystectomy. However, the present author contends that such a decision is not safe because so many complications (e.g., stone in common duct, perforation of the gallbladder, carcinoma, empyema, etc.) may develop and threaten life. The patient's life expectancy would appear to be the decisive factor. If the patient has more than seven or eight years of life remaining, it would appear wise to remove the gallbladder. On the contrary, if the patient has severe nephritis, hypertension or some other severe disease which is apt to cause death in 2 to 3 years, no operation should be performed. It is not difficult to determine life expectancy if no serious diseases are present, because actuarial tables are available to predict life remaining.

Residual stones in the common duct after cholecystectomy with or without choledochostomy are embarrassing to the surgeon. In general, the author believes the decision to reoperate on the patient to remove the stone is very often made too rapidly. First, it is often very difficult to distinguish such shadows from air bubbles; much care must be taken to eliminate air bubbles. Delay in operation often eliminates the necessity of operation, although it is realized many "pressures" exist urging reoperation. Over a seven-year period, Cole and Harridge[7] encountered 9

patients who 10 or 12 days after cholecystectomy and choledochostomy had a shadow resembling a residual stone in the postoperative cholangiogram. Operation was delayed and they were treated with 2 or 3 gm bile salts per day. This was done *only* in patients with a common duct sufficiently patent to allow continuous clamping of the T tube. If jaundice is present, or clamping the T tube produces pain indicative of obstruction, operation will be indicated. In 7 of the 9 patients the shadows disappeared in 8 to 31 weeks. In two patients in whom the shadow persisted longer than six months operation was performed. A stone was found in both of these patients and removed. We have no proof that all these shadows were stones. We suspect at least some were stones and either they passed through the sphincter of Oddi as they were, or disintegrated so that the fragments were passed.

Stenosis of the sphincter of Oddi is a disputed lesion; many surgeons doubt its existence. However, the present author has seen so many patients (75 to 100) in whom a probe or scoop could not be passed through the sphincter of Oddi that he is convinced of its validity. Part of the obstruction may be spasm, but fibrosis is often present; on some occasions the sphincter appears to be hypertrophied, although little fibrosis may be found. One of the best studies of this lesion was the initial one of Cattell and associates years ago. In their series 55 per cent had jaundice or a history of jaundice. Dilation of the common duct was noted in only 35 per cent of patients. The diagnosis is made by inability to pass a probe or scoop wider than 3 mm. in diameter through the sphincter. It is often difficult to prove that the probe has passed through the sphincter. The best way is not palpation, but observation of the end of the probe. If it has passed through the sphincter, one will be able to see the metallic color of the probe through one wall (anterior) of the duodenum but not through two walls. If the probe is pushing two walls of the duodenum anteriorly, one will see only a bulge and no metallic color (Fig. 5).

If there is doubt about the passage of the probe through the sphincter, the duodenum should be opened anteriorly. If there is obstruction, the opening at the sphincter may be so small that the probe cannot be seen. Insertion of a curved mosquito forceps through the opening will contact the probe; the opening should be dilated until the probe can be passed through the sphincter. The author believes that the sphincter should be incised, preferably anteriorly. Incision posteriorly is apt to open into the peritoneal cavity, causing a leak which if undetected and unrepaired will result in peritonitis. A T tube should be left in the common duct, but the distal arm of the tube should not extend beyond the sphincter, because pressure of the tube appears to increase the incidence of acute or subacute pancreatitis postoperatively.

Operations on the Biliary Tract

Obviously there is not room in this presentation for description of operative technique, but a discussion of certain operations including indications, usefulness, etc. appears pertinent.

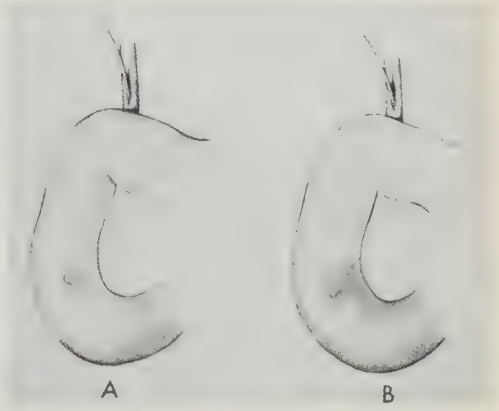

Figure 5. Mechanism for determining whether the common duct or probe has passed through the sphincter of Oddi. *A*, If the scoop has passed through the sphincter of Oddi the metallic color and outline of the tip can be seen. *B*, If the sphincter is obstructed by fibrosis, pressure of the scoop forward will press both walls of the duodenum anteriorly, but the metallic color and outline of the tip of the probe or scoop cannot be seen. (*From* Cole, W. H.: Precautions and errors in surgery of the biliary tract. SURG. CLIN. NORTH AM., 38:217, 1958.)

CHOLECYSTOSTOMY VERSUS CHOLECYSTECTOMY. As noted previously, it is natural that cholecystostomy should be developed and used before cholecystectomy (as it was). However, the high incidence of recurrence of symptoms and pathology following the former raises the question as to whether or not it should ever be used now that operability and technique are quite well understood. The truth is, however, that many elderly patients who have an acute cholecystitis (especially if perforated or threatening) will be so ill that cholecystectomy will be dangerous. Cholecystostomy requires far less dissection, is much less traumatic, and requires less time. Naturally we would like to do a cholecystectomy in an elderly patient and save him or her a possible second operation later, but we must remember the quotation used by numerous surgeons, "whatever operation you do, don't choose one which the patient cannot tolerate." In other words, on many occasions skillful technique cannot overcome a near hopeless operability. Glenn,[9] who has maintained an aggressive attitude in acute cholecystitis during the many years past, reports that he and his hospital staff performed 291 cholecystostomies in 2087 patients with acute disease (14 per cent).

CHOLEDOCHOSTOMY. Opinions vary among surgeons as to how often choledochostomy should be performed during cholecystectomy. Some perform an operative cholangiogram on most patients and open the duct only if stones are found or a history of jaundice is present. The author summarized the records of six surgical groups, including the University of Illinois, and found that the frequency of opening the common duct varied between 10.5 and 45.7 per cent (average 24 per cent), finding stones in 36.7 to 69.1 per cent (average 53 per cent) of ducts explored. The per cent of stones found in the total number of patients having cholecystectomy varied between 7.2 and 16.8 per cent (average 10.9). The surgical group having the highest incidence of choledochostomy did have the highest incidence of stones in the total number of patients, but the lowest per cent of stones in ducts explored.

Nearly all surgeons do a postoperative cholangiogram before removing the T tube. Perhaps the majority of surgeons insert a T tube after choledochostomy, removing it in 12 to 15 days unless suspicious shadows are seen in the cholangiogram (the present author agrees). Some surgeons close the incision in the common duct without a T tube for drainage. The author is strongly opposed to this because of the danger of leakage of bile through the closed incision, which is apt to happen in a small percentage of patients. If bile leakage occurs and is not detected early, a serious bile peritonitis may develop, which is often fatal.

CHOLEDOCHODUODENOSTOMY. This operation may anastomose the side or end of the common duct to the duodenum. Usually the side of the common duct is used because the original channel between the common duct and duodenum (through the sphincter of Oddi) is thereby left undisturbed. The operation is often used when an obstruction in the terminal end of the common duct is produced by a benign or malignant lesion of the pancreas. When a cancer of the head of the pancreas is present the gallbladder is usually intact. If so, a shunt between the gallbladder and duodenum or jejunum (cholecyst-duodenostomy or cholecyst-jejunostomy) will usually be performed.

One of the best indications for a choledochoduodenostomy is *recurrent formation of stones* in the common duct. Under such circumstances it is essential to eliminate the possibility of residual stones because there would be no indication for the operation (i.e., choledochoduodenostomy) under this circumstance. The possibility of a residual stone can be eliminated if ample negative cholangiograms are available after operation and/or there have been no symptoms of stones for two or three years beyond the original choledochostomy. In the author's opinion one of the most likely explanations of recurrent stones in the common duct will be obstruction or abnormal function of the sphincter of Oddi.

CHOLEDOCHOPLASTY. Fortunately strictures of the common duct are much less common than they were 25 years ago, due for the most part to the fact that cholecystectomies are now being performed by a higher percentage of trained surgeons.

Choledochoplasty, which is a relatively new operation, has undergone many modifications (Pearse Vitallium tube, Hoag operation, modified Hoag operation, Longmire operation, and others), but a simple anastomosis between the common duct and a Roux Y arm of jejunum (Fig. 6) appears to have survived the others and is the most popular. This procedure yields good results in 70 to 75 per cent of

patients. Almost all failures occur in patients in whom no stump of common duct is available, and the stump of the hepatic duct must be dissected out at the hilus of the liver to allow an anastomosis to the end of the jejunum.

Although many, many types of choledochoplasty have been suggested, the author knows of none which offers greater promise when the hepatic duct must be dissected out of the hilus of the liver than the one recently suggested by Cameron and associates.[2] In this procedure a hepatico-jejunostomy is performed, and before completion of the suture line a large caliber Silastic stint with multiple holes is passed through the anterior abdominal wall transhepatically into the biliary tract and through the anastomosis into the Roux Y loop. The stint is left in place 10 to 12 months.

Unsolved Problems

The two most important unsolved problems in biliary diseases are the *formation and dissolution of gallstones*. Perhaps our most logical factor in formation of cholesterol stones is a reduction in the ratio of cholesterol to fatty acids or bile salts (pioneered by Andrews, 1932) by absorption of bile salts through the gallbladder wall. A lot of theories modifying this concept have been suggested but there is not room here for their discussion. Infection appears to be important in the formation of calcium stones, but the important phase of formation of gallstones has not yet been discovered. During the past few years, one or two bile salts or acids (e.g., chenic acid) have been reported as being effective in dissolving stones in the human body. However, the percentage of failure is high.

Over the past several decades there have been numerous reports on formation of gallstones in rabbits (e.g., Hoffman and associates, 1968) and other animals. A recent report of particular interest is that of Carlisle and Tasman-Jones[3] in which they record that a diet containing 40 per cent casein, 15 per cent oleic acid, and 45

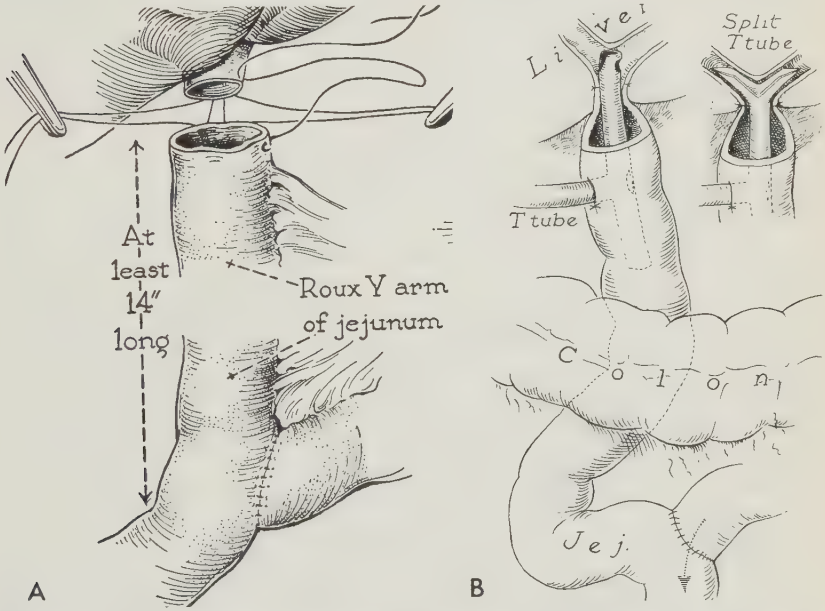

Figure 6. A common method of repair for stricture of the common duct. *A*, When the common hepatic duct protrudes beyond the hilus for several millimeters, the duct is anastomosed without a stent to the end of the Roux Y loop of jejunum with a very high expectation of cure. (*From* Cole, W. H., et al.: Strictures of the common duct. Ann. Surg., *133*:684, 1950, with permission.) *B*, When no duct protrudes beyond the hilus and it must be found by excising liver tissue at the hilus, edges of the duct are sutured to the end of the Roux Y arm of jejunum over a rubber T tube stent that is left in place 6 to 10 months to prevent stenosis at the anastomotic site. (*From* Cole, W. H.: Operative Technic. New York, Appleton, Century, Crofts, 1955, with permission.)

per cent laboratory pellets developed glycoallodeoxycholic acid and glychodeoxycholic acid gallstones. However, the oral administration of kanamycin prevented allo bile acid stone formation in the rabbits fed that diet. Could it be that antibiotics would slow up the formation of stones in humans?

Another difficult problem is *congenital atresia of the bile ducts*. When the intrahepatic bile ducts are present and the atresia is located in the extrahepatic duct, the outcome is good following anastomosis of the duct to a loop of intestine. However, fully 90 per cent of infants with this anomaly do not have patent extrahepatic ducts. Still more distressing is that very few of these infants have enough intrahepatic ducts to offer much hope of repair. Many surgeons have attempted to core out a segment of liver at or near the hilus, hoping to find a large duct or enough small ones to furnish enough bile to maintain proper function. Very few have reported more than rare success. Recently Kasai of Japan has reported that by coring out the liver at the hilus, and anastomosing this area to the duodenum or jejunum, he has obtained biliary drainage in about half his cases.

Carcinoma of the gallbladder must be listed as an unsolved problem because this tumor invades the liver extensively by the time diagnosis and resection are achieved. Even when resection of the right lobe is performed with the gallbladder, the cure rate is no higher than 5 to 8 per cent because metastases develop so often in the left lobe. When transplantation of the liver becomes feasible, with an insignificant percentage of fatalities due to the rejection phenomenon, then we may be able to obtain a respectable cure rate.

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This Golden Age of Surgery

*George A. Degenshein, M.D.**

There are very few professions where more disciplines are invoked than in surgery. Danger and discomfort have seldom dissuaded the surgeon. Under the Code of Hammurabi, circa 1950 B.C., if a nobleman lost the sight of his eye while under treatment, the surgeon's hands were cut off. If a slave died while under care, the surgeon was obliged to pay for the purchase of a new slave. In the sixth century, the Visigoths had a simple solution for operative deaths. They left the fate of the surgeon to the remaining family who, if they were satisfied would pay him, but if they were not, it was perfectly legal for them to have him put to death. So you see that malpractice fees in past history were much higher than they are today, and the number of surgeons was also somewhat reduced.

When Joseph Lister introduced his donkey engine to spray carbolic acid into the air of the operating room, no surgeon convinced of its value would reject it because of personal discomfort. When Sauerbruch introduced open thoracotomy before endotracheal anesthesia was known, he and his assistants worked in a stuffy, uncomfortable, negative pressure chamber without complaint. If someone were to prove tomorrow that we could reduce the incidence of wound infection significantly by all surgeons diving naked into a pool of foul smelling mercaptan solution before entering the operation room, I am sure that every surgeon worthy of that name would be ready to suffer the necessary consequences. Every house officer who has been frozen to a retractor for four or five hours understands the need for self-discipline. Now what is there about this brotherhood of ours that would prompt men to subject themselves to these disciplines? A look into the past may give us some clues to the answer.

When was the beginning? If one accepts the religious point of view, there is no question that God performed the first surgery when he resected Adam's rib to create Eve. If one does not accept the religious view, then the first surgeon was probably the first cave man who cut his foot on a rock and then found that he had to bind up the cut with some moss to prevent that sticky red stuff from leaking out and making him slip. As man evolved through the paleolithic and neolithic ages, he ultimately became a food gatherer and men gathered together into tribes. In the new stone age, a recent dig of a group of limbs revealed that 58 per cent of these limbs had fractures with excellent reduction. This is in keeping with evidence that early tribal leaders were not only responsible for being great warriors, but they also had the responsibility of caring for their wounded. Now, what are the earliest incontrovertible evidences of the beginning of surgery?

Figure 1 shows a skull dug up in Peru which dates back to the Inca Indians in pre-recorded history. The skull has at least five trephine holes, several with overgrowth of bone, proving that the patient did survive this operation. Whether this was done for headaches, epilepsy, letting evil devils out of the head, or was merely ritualistic, is speculative. At any rate, the early beginnings of medicine and particularly surgery are steeped in mysticism and magic. One thing is clear: the medical

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Figure 1. A skull, dug up in Peru, dates back to the Inca Indians of prerecorded history.

man was usually a member of the establishment and had the protection of the tribal leader, the king, or the church. Our current medical men are descended from the Shaman, or medicine man, who was not only responsible for the health care of the community, but was also responsible for winning wars, successful crops, appropriate marriages, satisfactory weather, and many other things.

Throughout the early centuries, the surgeon, on the other hand, was usually an itinerant who did his nasty job and then left town quickly before the final complications were evident. With the lack of anesthesia, very often men from the lowest ebb of society were the only ones with the necessary intestinal fortitude to carry out operative procedures.

We do have documented evidence that the early Egyptians and the Hebrews practiced circumcision and cataract surgery. The earliest surgical document that we have is the Edwin Smith Papyrus recently translated by Henry Breasted. This was dug up in Egypt from the tomb of a scribe who, in approximately 1750 B.C., was copying a Papyrus which was some 1300 years old, and when he died they buried the Papyrus with him. It is a collection of 48 case histories, mostly of trauma, but also involving breast cancer. It is thought to have been written by Imhotep, an Egyptian physician deified. There is one critical clue that we find in the Smith Papyrus that explains the attitude toward surgeons as opposed to the medicine man. The surgeon had three alternatives when he saw a patient. He could say that the patient could be cured, and therefore should be treated; or he could say that the patient could not be cured with surgery, and therefore he was not allowed to treat. The relief of suffering and pain without cure by surgery had no value. The surgeon's third alternative was to claim that he needed further time to observe the patient to determine curability. When he said he could cure, the surgeon was making a contract. If he kept his bargain he was paid; if not, he was punished as has already been noted in the Code of Hammurabi.

The next significant group who practiced organized surgery were the Greeks, and to this day most of our present terminology, precepts, systems, and codes date back to early Greece. On the second pillar of the Temple at Epidaurus, you can still read carved in the stone on the second steele a case history dated 400 B.C. of a traveler who was seized with a pain in his stomach due to a ruptured ulcer. An Aesculapian God appeared and ordered the patient's followers to hold him to the ground, whereupon Aesculapius opened his belly, cut out the ulcer, sewed him up, and sent the traveler on his way. Not only is this a vivid description of the first wedge resection of an ulcer, but note the modern touch of early ambulation, "and the traveler continued on his way." Aesculapian Temple medicine was a father and son affair. Aesculapian Gods built these magnificent temples (Fig. 2) where the

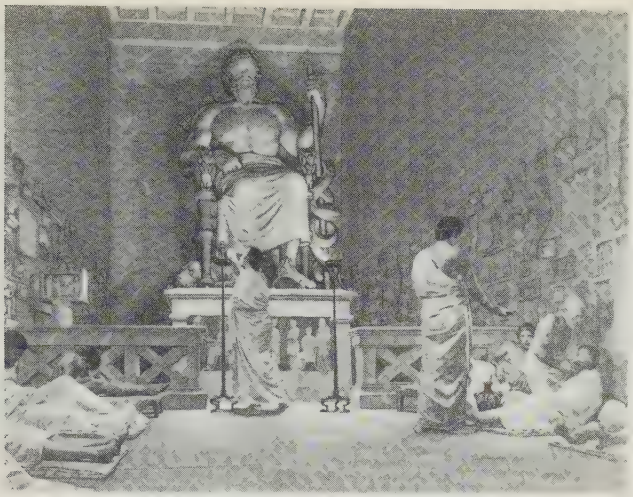

Figure 2. Early Greek Aesculapian temple.

patient would enter and would be given a soporific at night. During the wee hours of the morning, an Aesculapian physician appeared, usually with a basket of snakes on his head, and would reach over into the stall, where the patient was tied to a brass door knocker, and touch the part that hurt. The patient awoke in the morning supposedly cured. One of the fascinating things about Aesculapian Temple medicine was that if an affluent patient did not find the time, he could send a servant to lie in the temple for him and receive the treatment. In the early years of Aesculapian Temple medicine, there was no pay for the physicians except for gifts of foodstuffs. Ultimately, the patients gave votive offerings depending on their affluence. If an arm was healed, the poor patient would give a clay votive offering of the arm, whereas an extremely wealthy man might well give one of gold.

Space does not permit an elaboration of the early years of surgery, but for those who are stimulated to read about our forebearers, I envy them the pleasure of meeting for the first time Albucassis who stapled bowel together by having beetles bite the two edges of the anastomosis and then cutting off their bodies, John of Arderne, Jerome of Brunschwig, Guy DeChauliac, Gilbertus Anglicus, and a host of others. They will delight at Maimonides' description of Rhazi's rule which dates to the tenth century. "If a disease is stronger than the patient, there is no hope that he will survive and no physician will help him. If the patient is stronger than the disease, then the patient will get well and the physician is not a very great help. However, if the strength of the patient and that of the disease are equal, then one needs a perfect physician who will not commit errors to weaken the patient and throw the balance the wrong way." Much food for thought when we think of the era of blood-letting when even poor George Washington was bled to death by too many consultants, each of whom advised drawing off another pint of blood for his pneumonia. When we think of the tons of antibiotics used indiscriminately and the other iatrogenic complications for which we are responsible, Rhazi's rule stimulates personal reflections.

A word about the early origin of hospitals. Although hospitals existed as far back as the fifth century B.C. on the Island Ceylon, and there is evidence of one in India as early as 260 B.C. under the emperor Asoka, hospitals, as we know them today, did not exist before well into the Christian era. The Aesculapian temples were not really hospitals, and those at Epidaurus, Pergamon, Cnidos, and Cos usually gave only overnight care. In the early Roman era there were the Valetudinaria, which were originally hospitals for slaves, and the treatment was also in the hands of slaves, but still did not reflect the type of hospitals we have today. The first actual hospital in the Christian era was the Hotel Dieu founded about the sixth century by Childebert I, King of Franks, on the plea of his wife Clotilde. The Hôtel Dieu in Paris was started in 660 A.D. at the plea of St. Landry who begged for a hospital for the victims of an epidemic of plague (Fig. 3).

Figure 3. Medieval Hôtel Dieu, Paris.

The true continuity of hospitals as we know them today started with the crusades. In the 11th and 12th centuries when the Holy Land was invaded, many Europeans set out to make the trip to Jerusalem, often for cure of disease. These long treks required overnight stays either in the field or more often the travelers would seek a small town where they would be put up at the church. Eventually, the church set aside little houses which they called hospices. On many occasions, the pilgrim could no longer continue his or her journey and would have to remain in that hospice until death. The sisters gave nursing care, but it took centuries before any physicians were sent into these hospices, for who would interfere with the will of God? If an individual was sick, it was God's will and one could not tamper with that. Ultimately, it became inevitable that medical care and surgery was introduced. Despite this development of hospitals, they were primarily for the underprivileged, since for the affluent hospitals did not exist. When they were ill, they converted the home to a hospital and attending physicians and nurses were on hand at all times. The early hospitals such as the Hôtel Dieu in Paris had huge cubicles, each of which contained a large bed (see Fig. 3). In each bed there were six to eight patients, mixing men, women, and children in that same bed.

Enough of a morsel to tempt the reader to investigate the past, and now for the development of the background for this Golden Age of Surgery.

In the past 100 years, more dramatic advances have been made in surgery than in all of the thousands of years of history put together. Three basic problems had to be solved: (1) hemostasis, (2) anesthesia, and (3) control of infection. In this atmosphere it became evident that an understanding of blood, fluid and electrolyte balance had to be developed. The ultimate and easiest part of the recent Renaissance of Surgery involved the development of special surgical techniques and procedures for specific surgical diseases.

HEMOSTASIS

The modern day father of surgery was Ambroise Paré (Fig. 4). He lived in one of the most exciting times of all of history. It was the time of Raphael, Titian, Luther, Erasmus, Calvin, Vesalius, Paracelsus, Catherine DeMedici, and the Huguenot Rebellion. It was the time of the introduction of gunpowder into combat. Throughout the Middle and Dark Ages, the influences of Hippocrates and Galen were so great that when Vesalius proved that Galen's description of the hip bone was improper, the traditionalists insisted that it was because men wore tight trousers and, therefore, the hip bone at that time was different than at the time of Galen.

Paré broke with Galenical tradition by his condemnation of cauterization of wounds and popularization again of hemostasis by ligature. Paré entered the army as a barber surgeon after three years at the Hôtel Dieu as a pupil dresser. He was

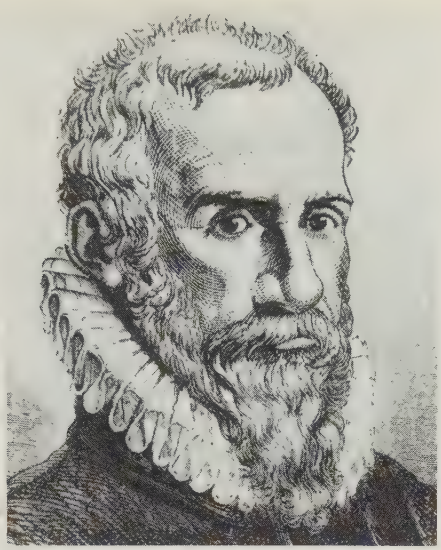

Figure 4. Ambroise Paré—the father of surgery.

taught by army surgeons that the gunpowder poisoned wounds and the only way to overcome the poison was to cauterize the wound with boiling oil. One night, he ran out of hot oil because of the large number of casualties and more than half his patients were treated in desperation by a salve of egg yolk, oil of roses, and turpentine. He could not sleep that night for fear that all the wounds so treated would become poisoned and that his patients would die. To his surprise and joy, he found that patients whose wounds were treated with the salve were alert and out of pain, whereas those wounds which received the boiling oil were festered and swollen, and the patients were feverish and racked with pain. He swore never to use the hot cautery or the boiling oil again. Paré was an ingenious surgeon, a great humanitarian, and a humble servant of his profession. On his statue is inscribed this favorite expression. "Je le pensay, Dieu le guarit." "I dress the wound, God heals it."

One of the fascinating stories about him is that of Colonel DeBrissac, who was wounded in his shoulder with a metal ball. After three surgeons probed for the ball and could not find it, they were faced with the possibility of destroying the shoulder merely to find the metal ball. Paré was called and simply asked DeBrissac what position he was in when he was hit. DeBrissac described that he was lying on his abdomen, arm extended, about to shoot off his own blunderbuss when the ball entered his shoulder. Paré then turned DeBrissac into the same position, straightened his arm, reached in, and in seconds pulled out the ball. On the battlefield, he was considered the equivalent of ten thousand troops, for the soldiers knew that their chance for surviving a wound was greatest with Paré.

Although he was surgeon to four French kings, he was considered nevertheless a barber surgeon and suffered greatly at the hands of his colleagues of the long robe. In Paré's time there were three echelons of practitioners. The physicians were learned men at the top of the profession who carried high social status, but practiced no surgery. They read and wrote in Latin. The intermediate group were the surgeons of the long robe who were members of the confraternity of St. Côme. These men did little actual surgery, but they prided themselves in their ability to read and write Latin. At the lowest end of the scale were the barber surgeons who evolved from the profane and vulgar, and were employed in earlier centuries for the tonsorial and blood-letting duties prescribed by many orders. They flourished after 1163. At the Council of Tours, Pope Gregory III abolished all surgery for monks. This was distressing to the rather intelligent group of monks who were carrying out the surgery for the nobility and they also had control of the public houses as well. The monks, in order not to be put out of the picture completely, designed a system

where they stood in their long robes in a pulpit, and they developed barber surgeons who stood beneath them on the monk's instruction, and actually did the surgery on the patient. In order to distinguish their authority, the monks wore long robes and ordered the barbers to wear short coats. This custom evolved into the long and short robes just described in 16th century France and has been carried down to this very day; it is the reason that the attending staff wear long white coats, whereas the house officer must continue to wear the short white coat.

Although Paré started as a barber surgeon and was in constant conflict with the surgeons of the long robe, when his fame became great, he was grudgingly admitted to the College of St. Côme despite the fact that he could not read Latin. He committed the final breaking insult by publishing his works in French, something completely unacceptable to his colleagues. Etienne Gourmelen, Dean of the Faculty of Medicine, attacked Paré so bitterly that ultimately Paré responded with his famous "Apology and Treatise and Journeys into Diverse Places" wherein Paré gave all of his earlier experiences including those in battle and keeps referring to Gourmelen all through it as "mon petit maitre" and challenging him to give equal justifications for refuting the precepts that Paré had laid down, especially on hemostasis and ligature. Logan Clendenning has said, "If I had a son and he wanted to study medicine, he should begin on the Apology and Treatise of Ambroise Paré, because there is something in that book he would find in none of his texts, there is life".

Now what have we learned from the story of Paré? Just some entertaining history? Much more. Before Paré, there was cauterization for hemostasis. Paré brought back the ligature which we still use today. One cannot help but sense that there is a next step in hemostasis. Is it not conceivable that some day we will look back upon ligation of hundreds of vessels during an operation as a slow, tedious, primitive method of hemostasis. No less a man than Theodore Kocher searched for a solution which would control bleeding. What a challenge for the young surgeon today to develop a method of hemostasis for small vessel ooze which will eliminate crushing clamps and insulting bits of thread and the tremendous time consumption to handle this technical problem. What a challenge!

I feel compelled to add a personal debt to Paré. One night in my early years in practice, a pharmacist's son was brought to the operating room with a bullet in his foot. He had apparently discharged his own rifle accidentally. After probing the dorsal opening into the cuboid bone for half an hour, we could not locate the bullet. I told the resident the story of Paré and as I finished, light struck and we simultaneously asked the young man (who was awake under spinal anesthesia) the position of his foot during the accident. He was climbing the horizontal bar of a log fence and as he lifted himself on that foot, the rifle went off. We then sharply dorsiflexed the foot to the position of the accident, and lo and behold, the top of the missile became evident in the depth of the wound and was easily recovered.

ANESTHESIA

Until the introduction of anesthesia, surgery was barbaric and speed was the byword. Robert Liston set a world's record by doing an amputation in 33 seconds. It is reported that in addition to the patient's leg, he also took three fingers from the assistant holding the leg in the same fell swoop. There is little doubt that anesthesia is responsible for greater alleviation of the pain of mankind than any other combination of discoveries. Despite this fact, almost everyone involved in its development suffered personally.

In 1800, Sir Humphrey Davy introduced nitrous oxide, and soon after itinerant entertainers set up one night stops in small towns to demonstrate the comic effects of "laughing gas." It was not long before the youngsters took on the laughing gas for an exciting night out on the town.

On March 30, 1842, the first surgery was performed under ether anesthesia. James Venable was a young man with two tumors of his neck, but was fearful of the pain of surgery. Crawford Long had observed bruises without pain on himself incurred during ether inhalations. James Venable also indulged in the ether frolics and consented to surgery under ether. Long either was unaware of the impact of his

discovery or he was unable to publicize it. As a country practitioner, surgery was uncommon, and for the year 1842 he did three cases: two on Venable for his tumors and one amputation of fingers on a boy.

In 1846, after a considerable preliminary story too complex to retell here, William T. G. Morton, a Boston dentist, delivered the first planned ether anesthesia using a valved device at the Massachussets General Hospital. It had the setting of a theater drama. Morton was late because of a necessary repair of the valve. John Collins Warren, the surgeon, instructed his men to hold the patient down and was about to make the incision for a tumor of the jaw. Morton arrived at that moment and delivered a successful anesthesia. The patient awoke and when asked if he felt the operation he replied, "I felt as if my face had been scratched." Warren, aged 70, turned to the audience in the amphitheatre and announced, "Gentlemen, this is no humbug," an accusation made previously under less favorable circumstances. Morton patented ether as Letheon and eventually the patent was rescinded. He spent the next 50 years trying to reinstate the patent and ultimately died of a stroke at Bellevue Hospital in New York.

In 1845, 37 operations were done at Massachussets General; by 1898, 3700 were done. It was like opening a door into a corridor lined with hundreds of doors slightly ajar merely waiting to be opened. Surgery was on its way to science and art in a humane setting.

INFECTION

The third problem to solve to allow surgery to come of age was infection, and the names of Pasteur, Semmelweis, Lister, and Fleming stand for a long fight to introduce antiseptic surgery as well as control of established infection. Although Lister made a milestone contribution, he did start what appeared to be a fruitless hunt for some magic solution which would kill all germs in the atmosphere, and took some emphasis away from the care of the wound itself. We may still return to worship at the Shrine of Paré, for he cautioned the surgeon against picking up any tissue around the blood vessel to be ligated, for if he did it would become necrotic and cause wound infection. Halsted was one of the best executors of Paré's caution in that he did a large number of hernias each year with only a rare wound infection, and this was before the introduction of rubber gloves and masks.

With an understanding of the sources of infection, surgery came of age and the abdomen became the playground of the surgeon, especially now that he could obtain anesthesia and explore with conveniences never known before. It would, therefore, be interesting to scan through the development of gastrointestinal surgery as one of the lines that became possible with the solution of these three basic problems.

GASTROINTESTINAL SURGERY

The early history of appendicitis is interesting in that in 1735 at Guy's Hospital in London, Claudius Amyand removed a ruptured appendix in an incarcerated inguinal hernia. Recall that the following statement was made before the advent of anesthesia, "It was a continued dissection, attended with dangers on parts not well distinguished. It lasted nearly half an hour and the patient bore it with great courage. 'Tis easy to conceive that this operation was as painful to the patient as laborious to me."

The introduction of the Murphy button in the early 1900's by John B. Murphy of Chicago heralded a dynamic era of intestinal anastomosis. The method was simple, rapid, and had great appeal since it eliminated tedious suturing. Today the Murphy button has become obsolete and is an object of historical curiosity, but it saved many lives, and I am sure took a few while gastrointestinal surgery was coming of age. Just to prove that even Murphy's idea was not new, the following description of an Alder button is dated approximately 1200 A.D. "If some part of the intestine has gotten through the wound in the abdomen and is either cut across wise or lengthwise while the remainder remains uninjured, it should be noted if the intes-

tines is warm or cold. If it is cold, some small animal, like a puppy, should be killed and placed over the intestines until the intestines is vivified by the natural heat of the applied animal [this might be called the first warm lap pad]. Then a tube of alder is to be prepared, its peth hollowed out, and its bark removed. It is now to be introduced into the gut and be stitched into position with a small pointed needle carrying fine silk." The author then describes cleansing the intestine with warm water and "the patient is then laid upon his back and gently shaken so that the gut will fall back." The abdominal wound was kept open until the gut healed and then it was sewed up.

In antiquity the prime interest in the gastrointestinal tract was the introduction of vomiting. The techniques of court vomiters included the passage of cloth tubes toward the stomach. During the Renaissance, emphasis shifted to treating patients with strictures or malignant lesions of the esophagus. Willis devised a whale bone instrument for feeding, and metal tubes soon followed. The famed John Hunter exceeded all ingenuity with the passage of a dried eel skin.

During the 19th century flexible tubes came into use for evacuation of poisons, and washing the stomach became a health fad. Many spas were opened in Germany where the guest was subjected to a Rotorooter type of washout of the stomach using a rather stiff brush, and when the gastric mucosa was completely denuded and presented to the customer as the dirt being washed out of his stomach, he was well satisfied and paid dearly for this treatment.

It is claimed that Kushmal's paper on stomach tubes stimulated Theodor Billroth's interest in gastric surgery. In 1881 Theodor Billroth (Fig. 5), in Vienna did the first successful gastrectomy. In a letter describing the operation, he reports that one of his worries was, "whether the stomach would digest its own suture line." He also tells us that despite careful planning, the operation took, including the slowly induced anesthesia, one and one-half hours. (I wonder how long the average surgical resident takes for his first one, and then brags that it was less than three hours.) One other valuable fact that was brought out was the method of determining operability. The patient was anesthetized and the abdomen palpated. If the mass was mobile, it was considered operable and the abdomen opened; if it was fixed, celiotomy was not done.

Billroth combined pathology with surgery and founded a school which influenced not only the entire continent, but America as well. He was a daring

Figure 5. Theodor Billroth.

operator and an inspiring teacher. In 1872 he did an esophagectomy, and in 1873 a total laryngectomy. Despite his successes he remained humble and gave credit to his assistants. He was a full man of many talents who loved music perhaps better than medicine. His relationship with Brahms is well known, and it is said that after hearing that master's compositions he burned many of his own. The ultimate test of a good teacher is the quality of his pupils, as has been so capably pointed out by Dr. Wangenstein in his section in this volume. Billroth's included Mikulicz Czerney, Wolfler, Gussenbauer, Eiselsberg, and a host of Americans who came to observe him. Notwithstanding this remarkable history, we owe to Billroth an even greater debt. He was the first to publish his total surgical experience, including all of his failures as well as his successful cases. Thus he encouraged others to stand unashamed but humble before their colleagues and report their statistics honestly, a characteristic, which to this very day, separates the men from the boys.

The same year, 1881, Wolfler did the first gastroenterostomy, and except for Roux's En-Y modification, the technique has changed very little. The milestone provided by Ernest Miles in the abdominoperineal resection is a classic which has stood the test of time. It may shock many of us to read of Lord Moynihan's description of his observation of one of the abdominal perineal resections done by Ernest Miles. From skin to skin he said the operation lasted about one-half hour and it was almost as though the clock stood still.

The story of rectal fistula is a fascinating one, and brings us back to the fact that there is nothing new under the sun. In the year 1349, John of Arderne devised the rather simple method of curing the fistula-in-ano by fistulotomy, done with a wire passed through the fistulous tract and attached to a bow-string type of apparatus which, then allowed him to cut down on the tract itself. It is interesting that when John of Arderne published his findings, he had a picture on the frontispiece of a patient's derrière, showing the surgeon sitting there with his index finger ready to enter the rectum. The censoring fathers made him eliminate the drawing of the derrière, so that the final publication merely had the picture of a surgeon with his index finger high in the air, but no indication of where it was about to go. So much for 14th century pornography.

John of Arderne's work was lost, as very often happens, and the next time we have a rather interesting follow-up is during the time of Louis XIV, when he called his surgeon, Felix, and asked whether he could cure his rectal fistula. Felix agreed that he could but it would require six months of soaking by the King. The King agreed, and Felix went immediately to the jails in Paris and tried every imaginable method of curing the fistula on inmates, and eventually came up with a simple fistulotomy. Some six months after the request, he did operate on the king, who was cured, and for this he gave Felix an unheard of amount of money—estates and titles which followed his family down to the present day. There seems to be a tradition for the great regard that patients have for their proctologist.

A final reference to inguinal hernia. For more than 5000 years, hernia represented an enigma to surgeons. Ambroise Paré, in the 16th century, cried out against the gelders who used the punctum aureum—the gold string. The contents of the hernial sac were reduced with an external wand and the gold suture went from the skin, posteriorly around the sac, and out of the skin again. The suture was then tied tightly to cause inflammatory healing of the neck of the sac. The distal tissues sloughed and the gelders treasured the testicles, especially from children, which were used for wealthy clients to increase their virility.

The use of external crushing clamps reflects the sad state of management of hernia the same year that Eduardo Bassini submitted his article "Concerning the Treatment of Inguinal Hernia" to Archiv fur Klinishe Chirgie. He reported 262 cases, with a cure of 239 of 251 reducible hernias followed for from one month to four and one half years. There was one mortality from pneumonia on the fifteenth postoperative day. His conclusions were:

"The operation which I advise for radical care of inguinal hernia and which I might call a rational procedure is absolutely without danger. That one actually achieves radical cure with this operation in such a way that the patient is not only cured, but, does not have to wear a truss is shown by:

1. The mechanic of the operation.

2. 108 patients operated on and followed for one and a half years after operation were cured and do not wear a truss.

3. Twelve men now serve in the army and are able to take the strain of army life.

"Aside from that, the method leads to a fast cure and the patient recuperates in ten to twenty days. Although there are recurrences (7% for reducible hernias), the percentage is so small and they occur under such exceptional circumstances that the value of the method cannot be denied."

Padova, July 30, 1889

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Gastrointestinal Surgery for Intractable Ulcer

*Robert M. Zollinger, M.D.**

The 150th anniversary of the birth of Theodore Billroth, who performed the first successful gastric resection on January 28, 1888, will be celebrated in 1979. Although many different techniques have been introduced in the intervening 96 years, the name of Billroth is commonly used to designate the procedure whereby the remaining gastric pouch is anastomosed to the duodenum (Billroth I), or the duodenum is closed and the gastric pouch is anastomosed to the jejunum (Billroth II). The many variations of technique in the performance of these two principles of gastric resection for ulcer were in competition for years with gastroenterostomy for the control of the acid factor in patients with gastric or duodenal ulcer. The indications for surgery for the control of gastric hypersecretion associated with duodenal ulcer were markedly curtailed to approximately 10 per cent of all patients by the early 1930's. By this time the long-term, poor results of gastroenterostomy performed for marked gastric hypersecretion converted the majority of surgeons to some form of gastric resection.

The value of any surgical procedure has been judged according to a lowered mortality rate and a low, long-term rate of recurrence. Such guidelines usually did not portray side effects and limitations so often accepted by the patient as a good trade for intolerable ulcer symptoms.

Vagotomy

After World War II, the concept advocated by Dragstedt of controlling hypersecretion by vagotomy and antral drainage without sacrificing a portion of the stomach had immediate appeal.[1] However, it offered a challenge for change to those who had been satisfied with one of the many standards of gastric resections. Many feared the well-known higher failure rates following gastroenterostomy, and the reported disagreeable side effects, especially diarrhea, sometimes associated with vagotomy, and were hesitant to change from their long-established operative procedure to which they had become addicted during their residency training. Others compromised by combining truncal vagotomy with antrectomy (hemigastrectomy), followed by either a Billroth I or II procedure. Current interest involves a denervation of the fundic glands by parietal cell vagotomy, leaving the nerve of Latarjet intact to ensure contractile power to the antrum.[4, 5] Fewer side effects such as diarrhea are anticipated, since no drainage procedures or division of the pyloric sphincter are performed.

The pros and cons of a radical versus a conservative procedure, combined with a variety of vagotomies, made surgeons more aware of the mechanisms responsible for the production of hydrochloric acid, before as well as after operation. While the mortality and recurrence rates for the various procedures were being documented by many observers, almost every clinic had a few patients who developed recurrent

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ulceration despite repeated surgical procedures of the classic type. There did not seem to be a logical explanation for these occasional failures, which at times tempted the surgeon to apply a different surgical technique to his subsequent patients.

Zollinger-Ellison Syndrome

A suggestion made in 1954 offered an explanation for some of these failures. Certain non-beta islet cell tumors of the pancreas were believed to produce such a potent gastric secretagogue as to cause recurrent ulceration, unless all of the acid-secreting surface of the stomach was removed by total gastrectomy. This was a different concept of the etiology of intractable ulcer, as well as a radical concept of treatment. The idea that the pancreas might play a role in the etiology of ulcer had long been accepted by physiologists and suspected by clinicians as they documented many earlier case reports. However, until this time, it had been assumed since 1927 that islet cell tumors either produced insulin or were nonfunctioning.

Time has dimmed the accuracy of recall of the exact course of events leading up to the implication of certain islet cell tumors in the production of a potent gastric secretagogue. In 1947, a patient had been observed in whom the gastric hypersecretion had persisted after vagotomy. At the time of the vagotomy a tumor of the body of the pancreas was biopsied. It seemed curious to have hypersecretion in the presence of malignant tumor involving the upper gastrointestinal tract instead of low acid values of achlorhydria. When the tumor was removed by hemipancreatectomy 10 days later, the acid values fell to zero. The true significance of this observation was not recognized at the time. However, several years later (1954), chance gave each my late colleague, Dr. Edwin H. Ellison, and myself within the space of one year, a patient with an ulcer problem of such persistent severity that each of us was chagrined by inability to control the acid factory by the usual radical surgical measures. Every surgical clinic has had one or more such patients who challenge the endurance of both patient and surgeon.

Dr. Ellison's patient was a 36 year old woman who had had a massive hemorrhage from a primary jejunal ulcer beyond the ligament of Treitz. After a local jejunal resection in July 1952, she promptly bled postoperatively and bled again in August 1952. In September 1952 she bled again, and this time a gastric resection was performed. During 1953 and the first half of 1954 she had four more gastric resections as well as a transthoracic vagotomy (elsewhere), leading eventually to a total gastrectomy. By this time the factor of a fulminating gastric hypersecretion was apparent since the patient's small gastric remnant produced 1625 to 4750 ml of gastric juice rich in hydrochloric acid over a 12-hour period. She died on June 7, 1954, and not until the microscopic report of the pancreatic tissue taken at autopsy was received was it apparent that the tissue contained tumor nodules of various sizes. The largest one measured 1 cm and was composed of islet cell tumor cells of the non-beta type.

In January 1954, a 19 year old girl was admitted to The Ohio State University Hospital because of severe vomiting and abdominal pain. During the preceding three years she had had an appendectomy in February 1952, a repair of two perforated jejunal ulcers in July 1953, and division of an adhesion to relieve upper abdominal intestinal obstruction in October 1953. The clinical significance of the perforated jejunal ulcers in this patient and the recurrent hemorrhage from the jejunal ulceration in Dr. Ellison's patient were not perceived at the time, although both patients were concurrently challenging our best efforts. The 19 year old patient had lost 53 pounds from her original weight of 180 pounds.

Because of her youth, the most conservative procedure possible was planned, but at the same time special measures were taken to control, if possible, the tremendous output of hydrochloric acid. It seemed a good idea to remove the greater curvature of the stomach including the fundus, where the major acid-producing folds were located, combined with truncal vagotomy, antrectomy, and a Billroth I anastomosis. The procedure was performed on January 28, 1954, leaving a lesser curvature tube 4×6 cm in size. A motion picture was made of the procedure because the case was so unusual. Within 10 days after operation, the patient's symptoms of burning had recurred, and already the output of gastric acid had returned to 29 mEq per liter.

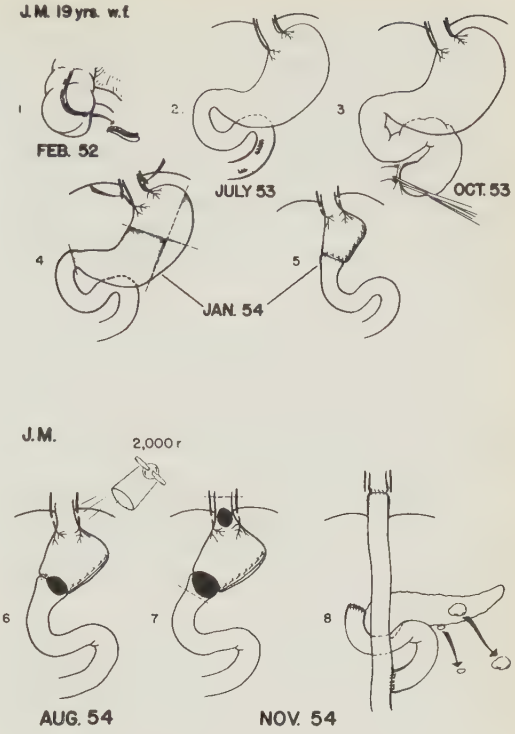

Figure 1. Outline of the various types of surgical and roentgenologic treatment carried out in one of the two initial reported cases. Islet cell tumor was found on the surface of the pancreas, with metastases in an adjacent lymph node at the time of total gastrectomy. From Homans, J.: A Textbook of Surgery. Ed. 6. Springfield, Illinois, Charles C Thomas, 1945; and Zollinger, R. M., and Ellison, E.: Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann. Surg., *142*:709, 1955.

For the next six months she followed her diet, gained weight, and was given vagal blocking agents. However, at this time 12-hour gastric aspiration showed 2000 cc of gastric juice with 32 mEq of free acid. In a desperate attempt to avoid total gastrectomy, the patient was given 2000 roentgen units of radiation to the gastric pouch in August 1954, without relief of the burning epigastric pain or a decrease in an ever-increasing output of gastric juice.

A letter was written to Dr. Hilger Jenkins, Chairman of the Motion Picture Committee of the American College of Surgeons, telling him of the failure of the operation we had hoped to present on the program. In his reply on August 5, 1954, he recalled a similar case of his own associated with "an insulin-producing islet cell tumor of the pancreas." He questioned whether our patient might have hyperinsulinism. Accordingly, she was fasted for 48 hours but her blood sugar never fell below 78 mg per 100 ml. She required narcotics for relief of pain during the fasting period. It was clear the patient did not have an insulin-producing tumor. It should not be forgotten that until this time, there were only two types of recognized islet cell tumors: those associated with hyperinsulinism and those considered to be nonfunctioning.

The patient was hospitalized for the sixth time in nine months in October 1954. On November 3, 1954 a total gastrectomy was performed. There was a large penetrating ulcer of the esophagus and a large ulcer involving the entire posterior gastroduodenal anastomosis. A direct end-to-end anastomosis was made between the esophagus and a Roux-en-Y arm of jejunum (Fig. 1). Because of Dr. Jenkins' suggestion, the pancreas was thoroughly explored for evidence of an insulin-producing tumor. Two small nodules thought to be lymph nodes were excised from the anterior aspect of the left side of the body of the pancreas. One nodule proved to be an islet cell tumor separated from normal pancreas by a thin capsule which was penetrated in places by tumor cells. The second nodule was a lymph node containing similar non-beta islet cell tumor cells.

The presence of metastases in the lymph nodes did not prevent the patient from mothering two children, five and seven years later, and she is now living almost 25 years later, working every day and free of symptoms. Ten years after operation, when the patient had a cholecystectomy for cholelithiasis, splenectomy and left hemipancreatectomy, there was no gross evidence of metastasis, but a small microadenoma was found in the resected portion of the pancreas without evidence of malignancy. The strange behavior of this malignant islet tumor and its metastasis may have fathered the idea that removal of the stomach or the end-organ in some way inhibits the further growth of any residual tumor.

These two unusual cases suggested a relationship between the enormous gastric hypersecretion, primary jejunal ulcerations, and non-insulin-producing islet cell tumors of the pancreas. An abstract was submitted for possible presentation before The American Surgical Association meeting to be held in Philadelphia in April 1955.[8] Acceptance of this abstract led to frenzied activity, trying to identify the non-beta islet cell believed to be responsible for the production of a potent gastric secretagogue. Ellison was tremendously stimulated by the concept and sought assistance from several pathologists, including Dr. G. Gomori. In addition, he evaluated the potential role of glucagon as the ulcerogenic factor. Glucagon was mentioned in the final paper, but this concept was the only source of complete disagreement between us.

A diagnostic triad was proposed consisting of: (1) primary ulcerations in unusual locations, i.e., second or third portion of the duodenum, upper jejunum, or recurrent stomach ulcers following gastric surgery short of total gastrectomy; (2) persistence of voluminous hypersecretion despite adequate conventional medical, surgical, or irradiation therapy; and (3) identification of a non-beta islet cell tumor of the pancreas.

The clinical syndrome was presented as a diagnostic triad in order to be consistent with the established Whipple triad associated with insulin-producing islet cell tumors. The presentation by Ellison was accepted with a response beyond our expectations! We were encouraged by the comments of those especially knowledgeable in pancreatic problems including Drs. Allen Whipple, Lester D. Dragstedt, Carl Moyer, Edgar Poth, and Hilger Jenkins.

In closing the discussion it was mentioned that "if these observations accomplish nothing more than a renewed interest in the ulcer problem with new avenues of study, we will feel justified in reporting these two cases." Little was it realized how prophetic these comments would be. Numerous reports in a variety of specialties have been published on the subject since that time.

Prior to this presentation, surgical physiologists had long been interested in the relationship between the pancreas and experimentally induced peptic ulcer. In 1948, Poth concluded "that both the internal and external secretions of the pancreas may be implicated in ulcer formation." Many clinical reports had called attention to the occurrence of peptic ulcer in association with islet cell tumors as well as with the syndrome of multiple endocrine adenomatosis.

After 1955, case reports supporting the concept of the ulcerogenic syndrome began to appear sporadically. The next five years were a period of challenge as a variety of explanations were offered as an alternative to the concept of an islet cell produced gastric secretagogue. In 1956, Eiseman and Maynard suggested characterizing the ulcerogenic triad with the eponym "Zollinger-Ellison syndrome." The identification of a possible gastric secretagogue produced by these non-beta cell tumors stimulated a search by many investigators.

The suspense was lifted in early May 1960 when a letter was received from Professor R. A. Gregory of Liverpool stating that he and his associate, Dr. Hilda Tracy, had found gastrin activity in islet cell tumor tissue equivalent to that in 35 to 45 times the tissue weight in hog antrum mucosa.[3] The ulcerogenic tumor had now been given international recognition. An era of confirmation followed as the number of case reports increased. Others promptly substantiated these findings. Finally in 1964, Gregory and Tracy published a summary of their work and concluded there was strong evidence that the active principles of ulcerogenic islet cell tumor was in fact gastrin, which had been isolated and named by Edkins of London in 1905.[2]

For a time the diagnosis of an ulcerogenic islet cell tumor was based on the criteria outlined in the original presentation. Improvements in diagnosis resulted

from laboratory studies which demonstrated that the stomach was producing acid to its maximum with little increase from histamine stimulation. The roentgenologists began to report their suspicions of a tumor when fluid retention in an unobstructed stomach was associated with marked thickening of the gastric folds. Subsequent studies have shown that these thick folds were the result of a trophic effect from a chronic hypergastrinemia. The duodenum tended to be enlarged with ulcerations in unusual locations such as beyond the ligament of Treitz.

The diagnosis became more certain when McGuigan, in 1968, reported the development of a sensitive radioimmunoassay technique for the measurement of the serum gastrin levels.[6] Within a short time this monumental contribution was to become widely available and serum gastrin determinations were to become almost a routine test in the evaluation of patients with gastrointestinal problems as well as those with endocrine disorders. The serum gastrin levels have been intensively studied in the animal laboratory as well as in patients following the intake of a variety of foods and drugs, and after surgical procedures.

Clinical Groups

Over the years, as the accuracy of diagnosis increased, the number of cases appear to fall into several clinical groups. In the first group are patients with a valid ulcer history or persistent diarrhea, laboratory findings of gastric hypersecretion, and x-ray evidence consistent with the changes seen in association with an ulcerogenic tumor, but only a slight elevation in serum gastrin levels. The second group is composed of patients with ulcer symptoms and elevation in serum calcium as well as serum gastrin. Two tumors, a parathyroid adenoma and a gastrin-producing tumor of the pancreas, occur in one-fourth or more of these patients. A third group includes recurrent ulceration after a standard sugical procedure for duodenal ulcer, which invariably raises the question of the presence of a gastrin-producing islet cell tumor. The fourth group includes those patients who easily meet all of the essential clinical and laboratory criteria described in the original ulcerogenic islet cell tumor triad. Repeat fasting gastrin levels including one or more provocative tests of calcium, secretin, or magnesium sulfate should precede the decision for surgery.

When the history and laboratory findings strongly suggest the diagnosis of gastrinoma, the patient and family should be thoroughly informed of the probability of total gastrectomy, splenectomy, partial pancreatectomy, and removal of involved lymph nodes or sizeable metastases in the liver. The finding of one endocrine tumor is a mandate to look for others in the same patient as well as in members of the immediate family.

Attention has recently been called to the fact that antral G-cell hyperplasia can rarely be responsible for gastrin elevations and symptoms similar to those produced by a gastrinoma. In these patients, the gastrin levels are depressed by the provocative secretin tests and decreased by a total meal. In such patients antrectomy rather than total gastrectomy may suffice.

Treatment

Total gastrectomy is no longer considered formidable; unfortunately, however, all too many of these patients have had one or more previous surgical procedures for recurrent ulceration. Evidence of hepatic or lymph metastases is sought, and the head, body, and tail of the pancreas are mobilized to ensure palpation of the pancreas between the fingers. Preoperative high gastrin levels in a patient with gastric hypersecretion, especially following a provocative infusion of calcium or secretin, is adequate proof of an islet cell tumor in the pancreas and justifies total gastrectomy. Serial resections of the tail and body of the pancreas searching for proof of tumor is no longer advocated.

A Roux-en-Y anastomosis is performed because it affords adequate protection against bile regurgitation, and postoperative nutrition is just as satisfactory as when pouches are constructed. The diet is increased to six small feedings a day, although eventually eating habits will not differ from those of a patient with an intact stomach. Patients are instructed to weigh themselves weekly and to avoid smoking and excessive ingestion of coffee or tea. B_{12} injections are required monthly for the rest of their lives. Approximately one half of the patients will

sustain ideal body weight. Those who lose or fail to gain weight should be evaluated with special attention to excessive smoking or coffee intake, evidence of stenosis of the esophageal gastric anastomosis, gallstones, or aggressive growth of the tumor with liver metastases.

Fasting gastrins are recorded at approximately six-month intervals. When the gastrin levels are increasing or the patient does not appear to be doing as well as expected, or metastases were found at operation, a provocative infusion study with calcium or secretin is indicated. The fasting gastrin does not always provide an accurate evaluation of the extent of tumor involvement, which may be reflected in dramatically high gastrin levels only following provocative infusions. When the gastrin levels exceed 1000 picograms, it is recommended that the patient have an hepatic angiogram. Approximately one-half of the patients will show hepatic metastases of varying size. Occasionally extensive metastases will be visualized despite relatively modest gastric elevations. Patients with hepatic metastases may survive for some years, since these carcinoid-like tumors may progress very slowly. Chemotherapy has been considered in recent years when hepatic metastases are verified. Irradiation of hepatic metastases has been observed to reduce the size of growth temporarily.[9]

Attempts were made to collect all the recorded cases, numbering approximately 800 by 1970. Dr. Stuart Wilson of the Medical College of Wisconsin maintained a registry of cases and reported his observations.[7] It became apparent that total gastrectomy as originally advised has withstood the test of time and should be carried out, even in the very young when the diagnosis was documented. Occasionally success followed removal of a solitary tumor such as occurs in the submucosa of the first portion of the duodenum in 10 per cent of these patients. Statistics suggest that recurrence can be anticipated in more than 50 per cent of such patients, since these gastrin-producing tumors tend to be multiple, and the incidence of malignancy with metastasis is high and may well exceed 75 per cent.

The ulcerogenic tumors are frequently described as carcinoid tumors which grow slowly but are usually multiple, the majority of which have a malignancy potential. Therefore it is prudent to leave the pancreas behind since it is almost impossible to remove the multifocal tumor sources of gastrin within the pancreas, or the regional lymph nodes or liver, which would continue to stimulate any remaining gastric acid-secreting surface. The concept of removing the end-organ and leaving tumor behind is contrary to the sound principle of surgery for malignancy, but in this instance it seems to offer the best hope so far of prolonged patient survival. The histamine antagonist H_2-receptor, such as cimetidine (Tagamet), has shown promise in controlling the marked gastric hypersecretion. The effectiveness of such drugs could result in the indefinite postponement of surgery, and the condition of poor-risk patients improved and possible complications avoided in those who refuse total gastrectomy.

Summary

Some of the questions regarding the ulcerogenic islet cell tumor syndrome remaining to be answered in the future might include the following: Will the histamine antagonist H_2-receptor decrease the need for surgery and avoid or safely delay total gastrectomy? Since the long-term postoperative serum gastrin levels tend to remain elevated, should chemotherapy be routinely utilized? Does postoperative hypergastrinemia play some role in sustaining nutrition to the patient after gastrectomy? Does the removal of the stomach (end organ) inhibit the further growth of retained islet cell tumor? Will the future clinical practice see the use of readily available immunoassays for the routine screening of patients with gastrointestinal complaints? Will the future see the control of gastric hypersecretion by hormonal measures?

The ulcerogenic islet cell tumor syndrome offers an explanation for some of the failures of previous surgical procedures. It has called attention to the potential of certain islet cell tumors of the pancreas to produce gastrin, a potent gastric secretagogue, in addition to insulin. Clinical and experimental studies have extended the known physiologic effects of hypergastrinemia including the trophic effect on the gastric mucosa as well as numerous other effects on the gastrointestinal tract.

The ability to measure the serum gastrin levels by immunoassay simplified the diagnosis of the ulcerogenic islet cell tumor and provided a diagnostic as well as a research tool to assess the effects of various food, drugs, diseases, and surgical procedures on the serum gastrin levels. This syndrome has played a role in creating a stimulus to study the possibility of isolating other gastrointestinal polypeptides and measuring their levels in islet cell tumors, as well as in gastrointestinal disorders. It would be foolish to accuse any islet cell tumor of the pancreas as being nonfunctional, since an ever-increasing number of tumor-producing polypeptides have been revealed and many others are under suspicion. The upper gastrointestinal tract, and in particular, the duodenum and pancreas, may be the richest source of hormones in the body.

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Half Century of Neurosurgery

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It is an interesting fact that wherever and whenever man began to use stone tools he began to carve holes in the skulls of his fellow men. This practice continued through the Bronze and the early Iron Ages but these early practitioners learned to leave the dura intact, as is indicated by evidence of subsequent bone healing in a surprising percentage of specimens recovered from caves and burial mounds. Neurosurgery, as a truly therapeutic field, could not develop until the days of asepsis, anesthesia, and the localization of cerebral function had been determined. Sir Victor Horsley of London, combining Ferrier's principles of localization with aseptic technique, in the 1890's began to establish neurosurgery as a branch of surgery. By the turn of the century his clinic had received American visitors including Cushing, Frazier, and G. W. Crile of Cleveland. It was Horsley who, because ligature was difficult, introduced the application of bits of muscle to control bleeding from the brain. He operated for brain abscess, brain tumor, cranial trauma, and tic douloureux. Ernie Sachs received his formal training with him and following World War I, Ernie became Professor of Clinical Neurosurgery, the first professorship in the world with this title. In the operating room Ernie's brittle temper was legendary. It is reported on one occasion, he ordered the orderly from the operating room and to speed his departure kicked him in the rear. When the orderly turned with his dukes up, Ernie retreated holding up his hands while saying "Don't touch me I'm sterile."

In 1900, Cushing returned from his tour of European centers to Johns Hopkins Hospital with the decision to limit his work to neurological surgery, and thus became the father of neurosurgery in this country. In 1901 he advocated the recording of blood pressure during operations with the new Riva-Rocci "machine." He described palliative decompression for malignant brain tumors in 1905 and developed silver clips for hemostasis in 1911. These early clips were simply cut from round wire and if they were squeezed a bit too hard they would go cross-legged. Cushing became professor of surgery at Harvard Medical School in 1912, leaving his assistant Walter Dandy at Johns Hopkins. From that time on Dandy became Cushing's outspoken opponent. Though not interested in pathology, Dandy far surpassed his early master in innovating procedures. It has been stated that no two men could have made such great contributions to the same field from more different approaches. Dandy described ventriculography in 1918 at which time Cushing considered it unnecessary and somewhat demeaning to the art. In the following year Dandy described pneumoencephalography, referred to then simply as encephalography because electroencephalography was not to be described until 10 years later (Hans Berger 1929–1938). Dandy made many friends, but few among his confreres. He was not asked to meet with the founders of the Society of Neurological Surgery in 1920, and when later invited to join he curtly refused.

When I attended McKeesport High School gaslights were in (including auto headlights). Saturday night was bath night, the movie theater was a nickelodeon, cream rose to the top, ladies let down their hair on going to bed, and if an automobile tire lasted 3,000 miles the owner bragged about it. Before I finished high school,

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both parents had died of tuberculosis, which later claimed the lives of our housekeeper and both of my sisters. I had been named William James Gardner, Jr. My father was a surgeon and a horse and buggy doctor until 1906, when he bought his first auto. The horses were then returned to the stable but came into use when snow arrived and made the driving of an automobile almost impossible. Father had graduated from the Medical School of the University of Pennsylvania in 1894, from which I was to graduate in 1924, and my son, William James Gardner, III, in 1954. With this, I wrote the dean that my old school was getting in a rut—graduating a Jim Gardner every 30 years. During the 1950's in the McKeesport Daily News under the heading "Fifty years ago Today," a brief note announced that Dr. Gardner had transplanted a nerve from a dog's leg into the arm of a man.

I received a B.A. degree from Washington and Jefferson College in 1920, and on graduating from medical school in 1924 was appointed to a two year rotating internship at the U. of P. Hospital. At that time the treatment for diabetes was a sugar-free diet and for pernicious anemia was blood transfusion. When Minot and Murphy's therapy of adding lightly cooked liver to the diet came into vogue, a Pennsylvania Dutchman arose in the meeting to announce that he had long since learned to feed such patients liverwurst. Each intern was required to spend 3 months in neurosurgery. On April 1, 1926, my turn came up, and I hated the thoughts of going on this demanding and unpopular service, since my plan was to practice general surgery as had my father. When I reported for duty at 7 o'clock on this April Fools Day, to my dismay I was greeted with the news that Frazier's assistant Dr. "Bunny" Fay had just left his service to spend 2 years in medical neurology with Dr. Spiller. Thus Frazier was left with only a green, unhappy, and uninterested intern. The service was extremely busy and I had to work day and night to keep up with the workload which, of course, included doing all autopsies. In those days, an applicant for internship, if married, stood virtually no chance of being accepted because obviously he wouldn't spend all of his time in the hospital. At the end of my three months stint, Frazier still had no assistant. Having become very impressed by his personality, dedication, and surgical skill, and being unwilling to see him have to break in another green, uninterested intern, I volunteered to spend my remaining three months of internship on his service. After that, the die was cast and I became his assistant for the ensuing three years at a salary of $125 a month.

In 1928, there appeared a very prominent lady from Chile with left tic douloureux upon whom Frazier had operated for right tic douloureux many years previously, dividing both the sensory and motor roots. She therefore had paralysis of all masticating muscles on the right side. Since her left sided tic pain did not involve the first division, the chief recommended his new subtotal resection of the sensory root, accepting the not too remote possibility of paralysis of her remaining muscles of mastication. On the morning of operation the air in surgery was electric. Dr. Frazier, proceeding very slowly and carefully, divided the lower two-thirds of the sensory root, leaving the motor root apparently intact, and on stimulation with the faradic current, the jaw snapped shut. So with a sigh of relief, he turned the closure over to me. When the drapes were removed, the patient's chin was resting on her manubrium. When Frazier saw this, he just about hit the ceiling. He called the dentist to wire her jaws shut so that he wouldn't have to look at the gaping mouth. Some 10 days later, to everyone's immense relief, the patient could contract her masseter muscle. The wires were removed and once more life with Frazier became livable. With his meticulous technique, the chief's usual operating time for this procedure was 1½ to 2 hours, but one of his early trainees, Max Peet, was able to cut his time down to 30 minutes. Also, about 1928, I assisted Frazier in an operation introduced by Pussepp of France which consisted of incising and draining the syrinx for syringomyelia.

With the closing of school, Frazier uniformly took off for his cottage in Maine and his former trainee, "Chubby" Grant, would take over the service. He then was neurosurgeon to the graduate school of the University of Pennsylvania. Soon Chubby likewise began to take his summer vacation in Maine, and during my third year, the service was left in my charge for the three months of summer. At that time, I had never heard of a patient suing his doctor. In 1926, the intravenous injection of 25 per cent glucose had begun to replace concentrated saline for

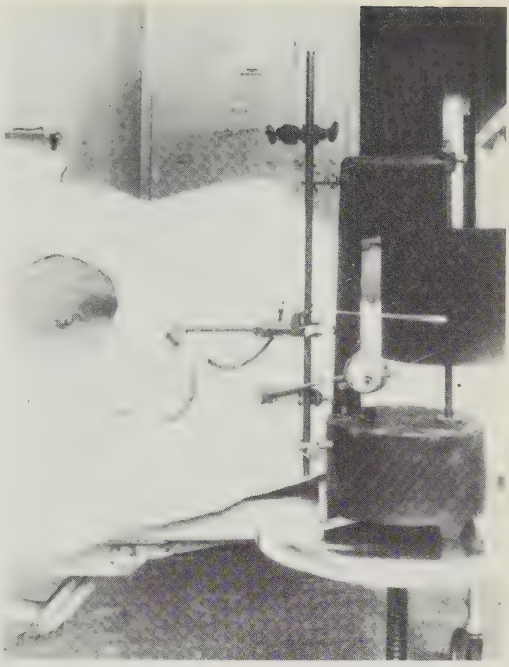

Figure 1. Few, if any, present residents have seen this method of recording pressures. Rotation of the drum was by a hand wound spring.

reduction of intracranial pressure. A method was devised to study its effect by recording the spinal fluid pressure on a smoked drum (Fig. 1). With this method the shape of the spinal fluid pulse wave was recorded and its amplitude was shown to be exaggerated in cases of increased intracranial pressure. This was attributed to less damping by the more tense spinal dural sac. The response to Queckenstedt's maneuver was recorded (Fig. 2), and the CSF pulse waves were shown to be abolished below the level of a subarachnoid block, whereas respiratory excursions were more prominent. Twenty-five per cent glucose by vein and concentrated magnesium sulfate by rectum proved to be only mildly effective in lowering CSF pressure for perhaps an hour.

At that time, Chubby had become a member of the Association for Research in Nervous and Mental Diseases which was having its annual meeting in Atlantic City in December of 1927, the subject being the cerebrospinal fluid. Frazier suggested that I have Chubby present my material to which I readily agreed, never having addressed such a distinguished audience. Chubby's presentation was well received. It finally appeared with his name as sole author in volume 8 of the 1927 proceedings of the association under the title "The Value of Hypertonic Solutions by Rectum or by Intravenous Injection for the Reduction of Increased Intracranial Pressure." Subsequently there was a change in Chubby's attitude toward me. There is an old adage that you instinctively dislike the person whom your dog bites.

During my training I never missed an opportunity to attend a consultation between Spiller and Frazier since, despite their respect for each other, there was almost certain to be an argument. This was particularly so when Spiller tried to tell Frazier where he should turn the flap in the case of a brain tumor. On one such occasion, following consultation, Spiller's patient arrived on the surgical ward with his head shaved and with the proposed osteoplastic flap outlined on the scalp with silver iodide. Frazier was furious and ordered me to remove every vestige of that tracing which, of course, was impossible short of scalping. In the operating room, the chief covered the tracing with tincture of iodine and then proceeded to outline his proposed incision by scratching with a scalpel. Needless to say it differed from Spiller's. In those days, for the patient who could pay, the cost of a bed in the 12 bed ward was $3.00 a day and a private room cost $10.00.

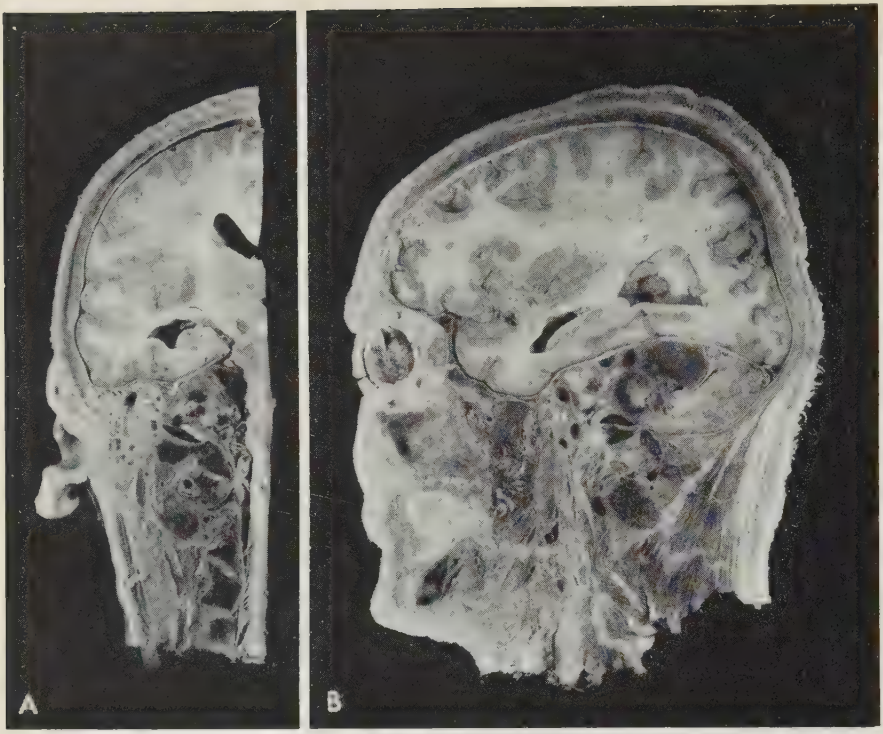

Figure 2. Coronal and sagittal sections showing bilateral eighth nerve tumors.

It was not uncommon for the patient with brain tumor to arrive on the service virtually blind from secondary optic atrophy from long-standing papilledema. The delay sometimes was occasioned by a prolonged course of treatment with bismuth and iodides in the hopes that the disease was syphilis.

In 1928, a patient was admitted totally deaf and blind from chronic papilledema. He was accompanied by a younger brother, Jess, who was also losing his hearing and who brought with him a genealogy chart, showing that bilateral deafness had been transmitted through three generations. The patient proved to have bilateral acoustic tumors and died following an intracapsular enucleation of his huge right-sided tumor. Autopsy disclosed the bilateral eighth nerve tumors with the histologic picture of neurofibromas of von Recklinghausen's disease. Dr. Frazier granted me two weeks leave to go to the village in Pennsylvania to study this family. I took with me a Barany chair, an ear irrigating set, and a set of tuning forks. With the aid of Jess, the family was investigated and the condition was found to have passed through five generations.

Information regarding the two earlier generations was provided by Aunt Maggie, the only living member of the third generation. She had a remarkable memory, being unable to read or write because her deaf father kept her out of school and constantly at his side because he had learned to read her lips and she translated the speech of others for him. Aunt Maggie told me that her paternal grandfather had moved west, perhaps to Ohio, in 1850 with 11 of his 12 children, leaving her father, his oldest son behind. Jim married twice and had four children by each wife. Two of both sets of offspring became deaf and subsequently blind.

In 1930, with Dr. Frazier as co-author, this family was reported in the Archives of Neurology and Psychiatry under the title "Bilateral Acoustic Neurofibromas: a Clinical Study and Field Survey of a Family of Five Generations." Transmitted only by a deaf parent, it was found to have affected at least 25 of 59 such offspring who had attained the age of 20 years, at which age the deafness developed. Several years later, I operated upon a member of the seventh generation of this family

(Gardner and Turner, "Bilateral Acoustic Neurofibromas, etc., Arch. Neurol. Psychiatry, 44:76–99, 1940). Subsequently a female member of a lost branch of the family was discovered who had become deaf and whose mother had died deaf and blind. During the interview, in answer to written questions about her maternal grandfather, she replied that he had not been deaf. Since this was a true mendelian dominant character, I, of course, questioned her on this point. She replied "I ought to know. I spent my summers on the farm with grandpa and grandma, and grandpa had perfect hearing. I recall it so distinctly because grandpa's brother, who lived with them, was deaf as a post."

One member of the fourth generation interested me particularly because at age 55 she had been totally deaf for 35 years but had no other symptoms, although her vestibular responses were absent. I, therefore, made Jess promise to phone me immediately upon Aunt Fanny's death so that I could come to perform an autopsy. Several years later Jess wrote to me in Cleveland that Aunt Fanny had died, but six weeks had passed before he had heard of it and therefore he was writing instead of phoning me. Still determined to get an autopsy I phoned Jess that I was coming and took off immediately for the 300 mile drive in my rickety Chevrolet. I arrived on a Friday night and found that Jess had made arrangements for us to meet with her three sons, two of whom were dead set against violating her grave. The third son was beginning to lose some hearing and, having three children, was less adamant. Continued efforts the next day failed to get their approval and by evening of that day I finally discovered that their chief concern was the attitude that the neighbors might take to their allowing mother's body to be dug up and "cut up." I decided to attend their church the next morning, it being Sunday, and appraise the circuit riding preacher of the situation and try to enlist his support. At the end of his sermon, while making some announcements, he described the purpose of my visit and told the congregation that he was heartily in favor of it and stressed the importance of this investigation for future generations of the family. On leaving the church, I obtained the signed permission of the three sons to disinter the body and have it transported to the Geisinger Hospital for autopsy.

Armed with this permit I finally located the coroner, who had been out hunting rabbits. He agreed to disinter the body and bring it to the hospital. By that time, it was 8:00 p.m. and I had surgery scheduled back at the Cleveland Clinic for 8:00 a.m. the next morning. On removing the lid, the body was moldy and it became necessary to stand back and to turn on the electric fan. Pressed for time I was about to remove the head and carry it back to Cleveland in my bucket but something stayed my hand. I parted the hair, incised the scalp, removed the calvarium, discarded the markedly softened cerebral hemispheres, and found the hindbrain fairly well preserved. It was removed together with the petrous bones and the attached tumors, which were about the size of marbles. I replaced the calvarium, closed the incision, combed the hair, put the specimen in my bucket and took off for Cleveland. Some 10 days later, I received an apologetic letter from the undertaker requesting another $10 in addition to the $25 that I had already paid him, because of a situation that had arisen after he had reinterred the body: "Them two sons of hers come up over the hill wanting to see momma." So the undertaker had to disinter the casket once more and open it for the sons' viewing. Luck again was on my side.

A few years later, Jess died of malignant hypertension at the age of 55. He still had some hearing in his left ear. His older son had died in a Naval hospital of bilateral eighth nerve tumors. The widow shipped Jess' body to me. There were no skin lesions but his spinal nerve roots were studded with tiny neurofibromas. I removed his head and after thorough hardening in concentrated formalin, cut it in the sagittal plane with a band saw. One half was then sliced coronally and the other sagittally. It made a wonderful specimen. The tumors were larger than those of Aunt Fanny but there was no hydrocephalus or cerebellar hernia. Finally, in 1968, after several futile attempts, I succeeded in getting Dr. Eldridge of the Section of Genetics at the NIH interested in this family. This resulted in "Bilateral Acoustic Neuroma in a Large Kindred" (J.A.M.A., *214*:347–353, 1970). At this time the disease had been transmitted as an autosomal dominant through 10 generations.

During my period of internship, chloroform was no longer used and ether by inhalation, reinforced with novocaine containing some Adrenalin, was the preferred anesthetic for craniotomy. Later, the ether was combined with olive oil and

given by rectum. An endotracheal tube was not employed, nor was an intravenous started unless it became necessary during the course of the operation. If a patient's pulse ceased, he was dead. Circulatory stimulants were strychnine, caffeine, and digitalis. Tumor localization was made on the basis of a meticulous history and careful neurological examination including visual field study and a Barany test if the symptoms suggested a posterior fossa tumor. Spinal puncture was avoided in cases of papilledema. I recall one patient with papilledema and ataxia who had a suboccipital craniotomy for what ultimately proved to be a frontal lobe tumor. Occasionally skull films would disclose evidence of the tumor's location such as calcification, enostosis, or ballooning of the sella turcica. Ventriculography was resorted to for unlocalized tumors. Encephalography was not used at the University of Pennsylvania Hospital until 1928. Anesthesia was administered by nurse anesthetists and the sitting position was employed only in tic cases. At the end of this procedure Frazier would invariably ask how much ether had been required. Shaking the can close to her ear the anesthetist would tell him "about two ounces." Frazier frequently commented that in the sitting position the patient required less anesthetic. Exposure of the cerebellum was performed with the patient prone, the head of the table tilted up, and the patient's head flexed and supported on a padded oval face rest. Not infrequently, and despite a ventricular tap, the cerebellum would herniate on opening the dura.

On one occasion, Frazier returning from a visit to de Martel's Clinic in Paris related an incident in which this famous French neurosurgeon had led an 11 year old bare-footed girl clad in a scanty hospital gown, into the operating room. He had her straddle a wooden chair, cross her arms on the back, and rest her head on her forearms. Then under local anesthesia he carried out a suboccipital craniotomy for a cerebellar tumor. Frazier described this as a horrible exhibition. I didn't remind the chief of the problems we had with the prone position, with the unhappy anesthetist pouring ether while sitting on a stool beneath the drapes.

In 1928, Frazier sent me to New York to spend six months in pathology with Penfield and Cone at the Presbyterian Hospital. On the day of my arrival, to my dismay, I learned that they had just accepted an invitation to move to Montreal within a month. Despite the disorder created by their preparations to leave, this was a memorable four weeks that I spent with these distinguished teachers. They assigned me the study of babies' brains with hydrocephalus in which prior to removal, the CSF spaces had been injected with India ink. Among other things I discovered that the weight of these fixed brains exceeded the normal.

Many years later, I was invited to McGill to talk about syringomyelia, and in my suitcase I had placed an inflatable pneumatic splint which I had planned to demonstrate. On our way to the cafeteria we were joined by Penfield who, as I had observed before, walked with a slight limp. As he picked up his tray to take it to a table, he immediately put it down and grabbed his knee. People at once gathered around, and pulling up his trouser leg disclosed a rapidly swelling knee obviously due to spontaneous hemorrhage within the knee joint. This knee had been injured when his destroyer was struck by a torpedo in World War I. An orthopedist who was present ordered his immediate transfer to the hospital for the application of an elastic bandage. Having what I believed was a better idea, I quickly located my suitcase, extracted the pneumatic splint, and arrived at the hospital as Penfield was being transferred to bed. The splint was immediately applied without taking time to remove his trousers and inflated by mouth, with which Penfield sighed with relief. It developed that the chief of orthopedics was away but would return in the morning and I was to meet him at the bedside at 9:00 a.m. The splint was deflated and his trousers removed. The orthopedist aspirated several ounces of blood from the knee, after which Dr. Penfield requested the reapplication of the air splint. After returning home, at his request, I mailed him another splint and he subsequently told me he never left home without it. A few of the accomplishments of this great man are briefly reported in the September, 1976 issue of the Journal of Neurosurgery.

On his sensory homunculus, Penfield demonstrated that the area of cortex representing the snout is enormous. This area supplies sensation to the tactile hairs which significantly are embedded in erectile tissue, and are present in every mammal except man. This sensory area, therefore, has persisted during evolution

despite the disappearance of these effector organs. Assuming the erect posture, man began to use his forepaws rather than his tactile hairs for investigating his environment. It has been suggested that the paroxysms of tic douloureux, having the typical characteristics of a parasympathetic reflex, may result from cross stimulation of presumed parasympathetic fibers in the sensory root by a tactile impulse, followed by a secondary ephapse between parasympathetic and pain fibers (Clin. Neurosurg., *15*:1–56, 1967.)

On May 15, 1929, at the Cleveland Clinic, an explosion of some smoldering x-ray films stored in the basement of the outpatient building killed 126 people. Built in 1920, this building was a hollow square, four stories high, the roof capped by a skylight. It thus constituted a perfect set-up for the immediate and complete dissemination of the poison gas which, before the skylight blew out, was forced into every room. Seven doctors were among the casualties which included one of the founders and also Ted Locke, who had trained with Cushing, and was the first neurological surgeon in the state of Ohio. This accident led to the development of a new composition for x-ray films and to regulations regarding their storage.

In September, 1929, I presented a paper before the Pennsylvania State Medical Society meeting in Erie. The subject was the therapeutic effects of encephalography. As I stepped down from the podium I was met by Dr. Lower of the Cleveland Clinic who invited me to return with him to Cleveland to meet the clinic staff. I knew that they were looking for a replacement for Dr. Locke, and although I had other plans I accepted this invitation. During dinner with the Criles and the Lowers, Dr. Crile reminded me that some years previously, while visiting Frazier, he had observed me recording a patient's spinal fluid pressure on a smoked drum. As we parted that evening, Dr. Lower said he would call for me at 7 o'clock and take me down to meet the staff. However, we drove directly to the hospital where he introduced me to a patient with about a two weeks' growth of hair on her head and a tense, bulging right subtemporal decompression. He said that the general surgeon, Tommy Jones, had performed what he called a right subtemporal decompression for an unlocalized brain tumor, and asked me what I thought of the patient. I found that she had papilledema and although she understood the spoken word, she was unable to speak. I told Dr. Lower that she had a brain tumor in Broca's area. When he asked me where that was, I pointed to her left frontal region. Dr. Lower said "Would you like to operate on her?" I told him I would be happy to, but that was impossible since I must catch the evening train in order to get to Philadelphia by 7 o'clock the next morning where I had some cases scheduled. He replied, "Come with me" and led me to the surgical pavilion where an operating room was all set up for craniotomy with a sterile scrub nurse and a nurse anesthetist standing by. I subsequently discovered that Dr. Lower was not known as one "to buy a pig in a poke." Well again luck was with me. A left frontal osteoplastic flap exposed a large globular meningioma of the convexity that all but rolled out onto the floor. I finished the operation in 2 hours and 20 minutes, and the job was mine, and at a magnificent salary of $6,000 a year. Fortunately for me no one suspected that a terrible financial depression was going to hit the country some 30 days later. Five years after her operation, this patient brought to me her newborn infant with a hopeless myelocele.

Arriving at the Cleveland Clinic on October 30, 1929 (day 3 of the stock market crash) to take up my responsibilities, I found an upright Bucky diaphragm on the surgical pavilion used for making preoperative chest films, but which provided a perfect set-up for encephalography. Because the x-ray department, where ventriculogram films could be made with the patient horizontal, was far away in another building, it was obvious that the necessary transportation of the anesthetized patient, far from resuscitative measures, made ventriculography a hazardous procedure. As a result, encephalography began to be be employed even in patients with suspected brain tumor, although if papilledema was present, a precautionary trephine was made so that a ventricle could be tapped should it become necessary. I still had never heard of a patient suing a doctor.

The encephalographic picture of cerebellar tumor proved to be a lack of air in the ventricles, a filling defect in the cisterna magna and, on the anteroposterior film, the supracallosal sulcus was outlined in the midline. While operating upon one such case of presumed cerebellar tumor, exposure disclosed a congenital hindbrain hernia below which the spinal cord was cystic, an instance of pure

serendipity. It was decided that this patient's symptoms were due to syringobulbia with an associated asymptomatic syrinx. Six weeks later, a patient appeared with classical syringomyelia but with no hindbrain symptoms. Encephalography disclosed the same findings, and by 1950, the collapsing cord sign had been demonstrated in eight cases. This demonstration established that the cause of syringomyelia is not in the spinal cord but in the hindbrain. Twenty-five years after the first operation (J. Neurol., Neurosurg. Psychiatry, 28:227–259, 1965) the results of craniovertebral decompression were reported in 74 cases of syringomyelia, and pneumoencephalography was recommended as the best and *only* special radiographic procedure that should be used.

When neuroradiology became a specialty, Pantopaque myelography became the usual diagnostic procedure in cases of syringomyelia, and has remained so despite the fact that in a single series of 94 cases, Pantopaque has revealed the distended cord in only 34 (Major Probl. Neurol., *1*:57, 1973). The reason for failure is its heavy specific gravity, which may collapse the syrinx since it may be partly emptied in the head down position. Not only is the Pantopaque failure rate high in syringomyelia, but because of extensive narrowing of the spinal subarachnoid space, microglobules remain which may result in adhesive arachnoiditis and thus spoil an otherwise excellent postoperative result (J. Neurosurg., *41*:785, 1974).

It became increasingly obvious that the adult with syringomyelia has all of the pathologic findings of the infant with myelocele except an open neural tube. In describing "these watery tumors of the vertebrae" more than two centuries ago, Morgagni stated his belief that they result from the pressure of fluid descending from the hydrocephalic head through the tube of the spine where the bones are pressed asunder. During my intern days, and of course unaware then of Morgagni, I had encountered my first case of myelocele with hydrocephalus and at that time had considered this obvious cause and effect relationship. Over the years, it became evident that this conclusion of Morgagni was correct, whereas von Recklinghausen's theory (1886) that myelocele results from failure of closure of the neural

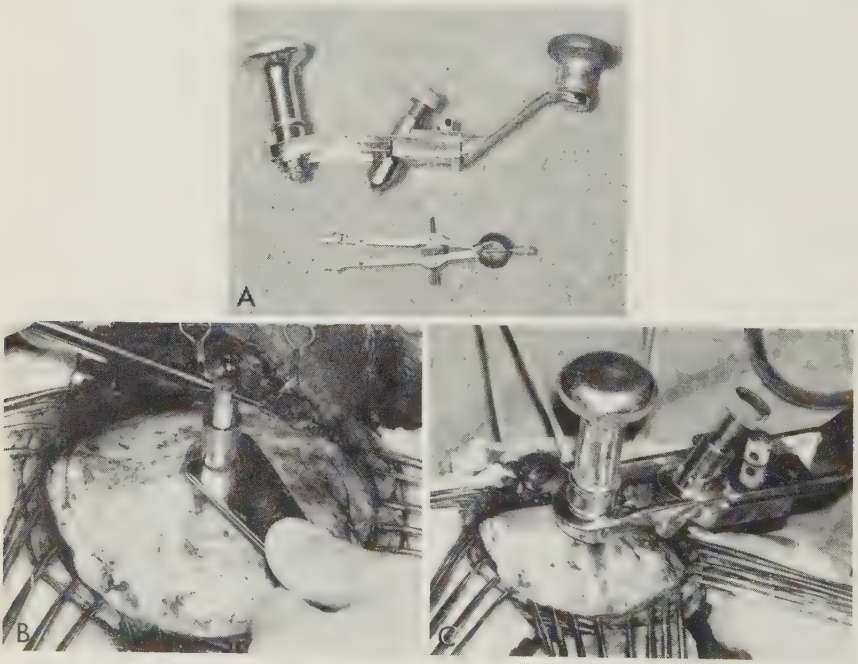

Figure 3. *A*, The compass is used to determine the proper location of the central drill hole. *B*, An expanding mandrel is tightened to fix it in the drill hole. *C*, The instrument is swung in circles as the cutting point is gradually advanced.

tube was incorrect. Furthermore it developed that all syringomyelia is merely symptomatic hydromyelia. An accidental discovery in 1973 further confirmed this fact when it was found that draining the elongated central canal at the tip of the conus would benefit the symptoms of both syringomyelia and syringobulbia (J. Neurosurg., 46:609–617, 1977).

Well to get back to my story, during my residency in Philadelphia, Bunny Fay had described to me a marvelous instrument called the Souttar craniotome, which he had seen on a trip to Seattle. With this it was possible to remove quickly a beveled circular section of the skull of any desired diameter. After arriving at the Cleveland Clinic, and unhappy with the drill and wire saw method of craniotomy, I recalled Bunny's statement. By this time Dandy had shown that an osteoplastic flap, totally detached from all vascular supply, would heal well and with a lower incidence of extradural hematoma. I, therefore, obtained a Souttar craniotome and had the mechanical department make an improved model. Rotating on a central pivot that was fixed in a drill hole, it quickly removed a beveled, circular piece of skull of any desired size (Fig. 3). As compared with the drill and wire saw method, it expedited craniotomy and reduced blood loss. I used this instrument throughout my 34 years with the Cleveland Clinic and also in my subsequent private practice until my second retirement in 1973.

As the Bovie electrosurgical unit described by Cushing (1928) came into widespread use, the need for Cushing clips became progressively less. About this time Percival Bailey, who had left Boston for Chicago, found it advisable to warn against the use of this cautery because of unwarranted damage to brain tissue. Rectal anesthesia by Avertin, which succeeded ether in olive oil, was widely used for a time but became outmoded by the development during World War II of intravenous sodium pentothal. Then the new specialty of professional anesthesiology came into being, accompanied by the routine use of the endotracheal tube. Now we have not only physician anesthesiologists, but when need justifies it, we find neuroanesthesiologists, neuroradiologists, and neuropathologists. Even in the great Cleveland Clinic, the anesthesiologist for a time refused to give a spinal anesthetic for a lumbar disc operation! Cushing, who insisted that the neurosurgeon should be his own diagnostic neurologist and complete boss in the operating room, would turn over in his grave.

In 1927, Egas Moniz had introduced the procedure of cerebral angiography. This was not readily taken up in this country until the less irritating medium, Diodrast, was developed, and which, in turn, has been replaced by still better media. At the beginning, the carotid artery usually was exposed by surgical incision under anesthesia. I well remember the first attempt at transcutaneous introduction of the arterial needle at the Cleveland Clinic. I and the head of the x-ray department undertook the procedure. It happened that when the intra-arterial injection succeeded, the film was not properly exposed and when it was properly exposed the needle was not within the lumen of the artery. After this fiasco, the procedure was delegated to our young associates. Who could have guessed that eventually arteriography and later the CAT scan would replace air in the diagnosis of hydrocephalus?

In addition to his arteriography, Moniz also was the first to treat mental symptoms by leucotomy. This was avidly taken up by others with modifications such as prefrontal lobotomy, undercutting, gyrectomy, and the simpler method of transorbital leucotomy of Freeman and Watts. Freeman used electroshock to produce unconsciousness in institutions in which the services of an anesthetist were not available to him. During World War II there were unfounded rumors that the Germans were using the latter method, which left no scar, to addle the brains of political prisoners and thus justify their confinement. Moniz received the Nobel Prize in medicine for his development of cerebral angiography and of psychosurgery. However psychosurgery was soon almost eliminated by the development of drugs for treating mental symptoms, just as the surgical treatment of hypertension by thoracolumbar sympathectomy or by Max Peet's splanchnicectomy (the present author performed 300 of these two methods) was eliminated by the development of hypotensive agents, unilateral nephrectomy, or by surgical improvement of renal blood flow. It was Harry Goldblatt, a Clevelander, who with the famous Goldblatt clamp, established impaired renal blood flow as a cause of renal hypertension.

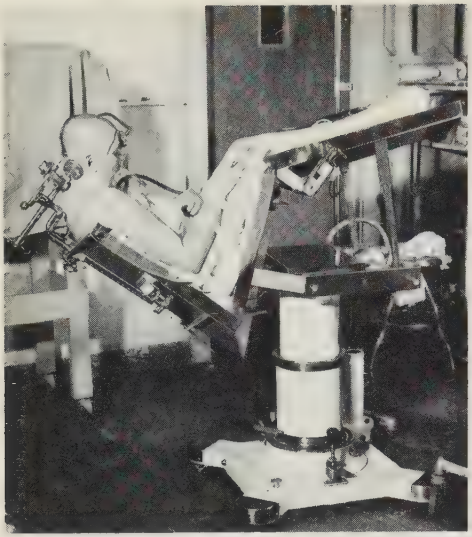

Figure 4. The conscious patient can aid in his transfer from the cart, after which the addition of a posterior head support permits cervical retroflexion for tracheal intubation. This patient was to have the right cerebral hemisphere removed for an infiltrating tumor.

The first opaque material for demonstrating the location of a spinal subarachnoid block was a French preparation known as Lipiodol. This heavy viscous material, injected in 1 to 2 cc amounts, was used solely to demonstrate the level of a spinal subarachnoid block. The exposures of course were made with the patient supine, so that the spine was close to the film. Some four years after Mixter and Barr's 1938 article had appeared describing protruded intervertebral discs as a cause of sciatica, Pantopaque became available. The early surgical treatment for sciatica was fusion of the sacroiliac joint or stretching of the sciatic nerve. The latter method was used because the straight leg raising test proved that the sciatic nerve was tight and therefore too short. I well recall one case in which Frazier, through a posterior thigh incision, exposed the sciatic nerve and lengthened it by hooking his fingers under it and pulling sufficiently to lift the leg off the table.

Following Wally Hamby's "graduation" from the Cleveland Clinic in 1935, a satisfactory craniotomy chair was finally devised. This unpadded stainless steel chair is shaped like a trough from side to side. The angle between the backrest and the seat is 67° and between the seat and the leg rest 120° (Fig. 4). Because of its shape, the patient is fixed in position by gravity with no need for restraints. The acute angle of the seat elevates the diaphragm and thereby reduces the degree of negative intrathoracic venous pressure. This chair can be tilted backward until the patient's feet are higher than his head. The use of this chair so facilitated posterior fossa surgery that the decreased morbidity more than made up for the slight risk of air embolism. During World War II, the clinical G-suit came into use. When inflated to 10 mm Hg with the patient in the posteriorly tilted neurosurgical chair, the problem of air embolism has been eliminated. If many years ago, the great clinic on our western prairie had accepted my suggestion to use this chair and G-suit they would not have published a series of alarming reports on air embolism in the sitting position.

The clinical G-suit saved the life of a wife of one of our staff. This woman, after delivery of a placenta percreta and following 11 hours of futile surgical efforts to control intraabdominal bleeding, had required 56 blood transfusions administered within a period of 18 hours. The surgeon finally concluded the operation so that the husband could have a last word with her. On being returned to her bed, she was placed in the G-suit at a pressure of 20 mm Hg (Fig. 5). This raised the blood pressure and to everyone's amazement it stopped the bleeding (J.A.M.A., *167*:985–986, 1958). The clinical G-suit is now used with gratifying success in the emergency treatment of ruptured abdominal aneurysms and other cases of shock from bleeding below the level of the diaphragm.

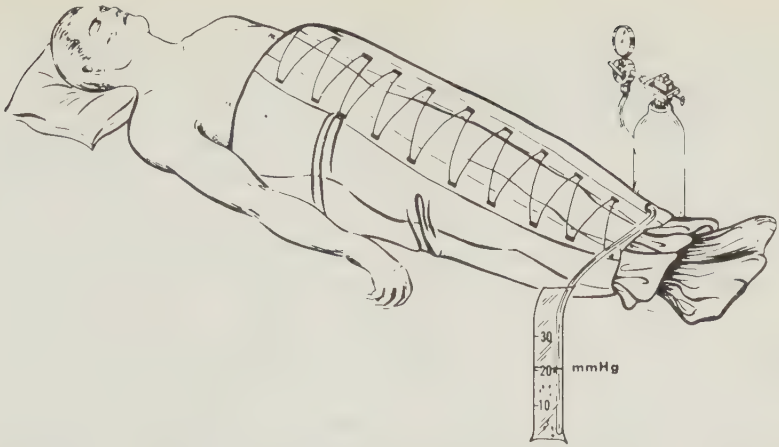

Figure 5. After the plastic G-suit has been inflated, the flow of air or of nitrogen gas is slowed until it escapes from the water escape valve only during inspiration.

Following Dandy's 1928 report, a right cerebral hemisphere was removed (J.A.M.A., *101*:823–826, 1933) for glioma with the patient in the craniotomy chair. It was found that the sitting position greatly simplified the operation in that, as the initial procedure, all venous outflow could be interrupted without causing venous engorgement or brain swelling. This facilitated dividing the corpus callosum after which the arterial supply could be easily exposed and divided without interrupting the circle of Willis.

In 1934, Tracy Putnam introduced endoscopic coagulation of the choroid plexus for hydrocephalus. This procedure was taken up at the Cleveland Clinic but without much success. However, it continued to be employed by Ted Scarf for many years with pretty fair results. Operations on the choroid plexuses, as first suggested by Dandy, have been replaced by the development of effective valve mechanisms which permit drainage of ventricular fluid into the right heart, peritoneal or pleural cavity. This last method was soon discarded because, for some reason, it resulted in a pleural collection of fluid with a high protein content. The first valve for hydrocephalus was devised by an engineer who had a child with hydrocephalus. Don Matson's drainage into the ureter after unilateral nephrectomy was popular for a time but given up because of salt depletion. For obstructive hydrocephalus, puncture of the floor of the third ventricle through the lamina terminalis still has an occasional advocate, whereas drainage of an obstructed lateral ventricle into the cisterna magna has about run its course. The reason for these failures is that congenital hydrocephalus is usually a combination of obstructive and communicating.

In 1943, Fulcher reported in the J.A.M.A. on the use of tantalum as a metallic implant to repair cranial defects. This material was popular for several years. With the development of sulfonamides it was used at the time of the initial debridement of compound, comminuted skull fractures. Following the introduction of antibiotics it was employed successfully in the primary closure of craniotomy defects resulting from excision of acute osteomyelitis and brain abscess. In these cases, if external drainage had not permitted secondary invaders, and if all of the infected bone was removed, the wounds healed without infection. It was found that bimetallism, resulting from the employment of other metals for fastening the tantalum to the skull, resulted in ultimate wound breakdown. This made necessary the development of tantalum screws. Tantalum has now been replaced by methyl methacrylate because of its radiolucency. However, the author continued to use tantalum in a thin sheet (0.007 inch) until his second retirement in 1973. The thin, partly radiolucent tantalum onlay could be fashioned at the operating table. It could be cut with bandage scissors, perforated with a card punch, and shaped with a ball-peen hammer on a hollowed wooden block to conform to the contour of the outer table, including the supraorbital ridges.

In 1946, in a patient with an olfactory groove meningioma, the first attempt to control intraoperative bleeding by inducing arterial hypotension, was described. A cannula was introduced into the radial artery and after the tumor was exposed the patient was rapidly bled 5 units of blood, which lowered the blood pressure to 80 mm Hg. The tumor was then rapidly removed with the electrosurgical unit and bleeding was easily controlled. After this tumor had been totally removed, four pints of her blood were injected in a retrograde fashion into the artery, restoring preoperative blood pressure. The remaining unit was placed in the blood bank. This method of induced hypotension was employed for several years. It was particularly effective in meningiomas because their nourishing extracranial vessels contract in response to blood loss, whereas the cerebral and coronaries do not (Surg. Gynecol. Obstet., *98*:343–346, 1954). This bleeding method was supplanted by the development of hypotensive drugs which are particularly useful in cases of intracranial aneurysms. It became known among Jehovah's Witnesses that I was willing to operate for brain tumor with the promise not to transfuse. I am convinced that transplanting of another person's tissue may cause complications that are not recognized as such.

On one occasion in 1946, while Al LaLonde and I were operating for brain tumor, a nurse whispered something in his ear. When I asked what she said, he told me that the patient upon whom we had evacuated a chronic subdural hematoma the day before was dying. I told him to go down and do a spinal puncture to rule out recurrent bleeding. Within a few minutes he was back to report that the man was in deep coma, with Cheyne-Stokes respirations and bilateral Babinski signs, but that the spinal fluid pressure was so low that it would scarcely drip from the needle. He was told that is something that can be corrected and he should repeat the spinal puncture and inject saline until the pressure was restored. He returned with eyes bugging out. He said that after injecting 60 cc the unconscious patient looked over his shoulder and said, "What the hell is going on back there?" From then on the compressed hemisphere was reexpanded during operation in each patient with chronic subdural hematoma.

In 1953, Palle Taarnhoj's operation of decompression of the sensory root for trigeminal neuralgia was first employed at the Cleveland Clinic. The results of this middle fossa approach confirmed Dandy's earlier conviction that the cause of trigeminal neuralgia is located in the sensory root. Palle then joined our staff and served for five years before returning to head his own unit in Denmark. A modification of his operation is still in use by Dr. Dohn at the Cleveland Clinic.

Well, having exceeded my allotted pages we will stop here. I now have an office in the Emeritus Department of the Cleveland Clinic with a wonderful secretary and don't have to do any work. However, I am still trying to convince teratologists that myelocele is the result of rupture of the closed neural tube and not its failure to close. I continue to write letters to editors urging the republication of Weed's, "The Development of the Cerebrospinal Spaces in Pig and in Man." Thousands of neurosurgeons are operating in cases of abnormal development of these fluid-filled spaces without knowing how this "third circulation" of Cushing develops in the normal.

The tremendous advances in the study of the patient with brain tumor, particularly the EMI scan and the surgical microscope, have revolutionized the practice of neurosurgery.

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Endocrine Surgery

*Oliver Cope, M.D.**

At the beginning of the 20th century, surgery of the endocrine glands had not been identified as a specialty. As the century progressed, new knowledge of diseases of the ductless glands appeared, demanding collaboration with many other disciplines. Surgery alone was proving insufficient. Special study clinics were frequently established; because the surgeon was essential to the establishment of the diagnosis as well as the treatment, the surgeon remained a key figure of the team and the surgical specialty of endocrine surgery evolved.

Decade by decade, one gland after another has been added to this specialty. The first diseases were gathered from older areas, the thyroid from general surgery, the ovary from gynecology, and the pituitary from neurosurgery. Then a host of new disorders were added, disturbances of the parathyroid, the adrenal medulla and cortex, islet cells of the pancreas, the thymus with myasthenia gravis, and more recently, carcinoid tumors of the chromaffin tissues and calcitonin secreting enlargements of the thyroid.

Originally all of the diseases included in endocrine surgery were treated by some form of surgical resection, partial or total. With increasing physiologic understanding of their etiology, some are now manageable by medical maneuvers, others by irradiation. A few are classifiable as psychosomatic and are passing from medicine to psychiatry. These last include Graves' disease and certain ovarian dysfunctions. For many others, however, no treatment other than surgery have been found and the specialty remains for the foreseeable future a full and active field of surgery.

The first gland to be resected for its endocrine effect was the testicle. In 1893 White reported bilateral orchidectomy in the treatment of prostatic hypertrophy.[36] Orchidectomy was also tried in 1903 for prostatic carcinoma,[38] but with the development of direct surgical prostatectomy in the early 1900's, relief of urinary obstruction was so much more effectively achieved that the endocrine procedure for both prostatic conditions was soon abandoned.

Removal of the ovaries was also carried out for the endocrine effect just before 1900.[7] By 1890 uterine fibroids had been observed to shrink following surgical removal of both ovaries and Beatson in 1893 removed the ovaries from two women with breast cancer.[7] The growth of the cancer was stayed in one, and slowed perhaps in the other.[7, 25] The effect subsequently was found to be so unpredictable that the operation was little used until revived in the 1930's.

To test the relationship of the ovaries to breast cancer, in 1928 Dr. Aub and his collaborators began by studying the growth process, principally the endocrine influences. The secretion of estrogen by girls was followed through puberty into adulthood. The patterns of ovarian function in women who developed cancer were measured. Once again, the removal of the ovaries was undertaken to assay its usefulness and the reasons for its failures. With the removal of the ovaries, the reduction in secretion of estrogen and progesterone helped only one third of the patients.[26] This unfortunate minority as we well know has been confirmed again and again, but bilateral ovariectomy still remains a useful procedure in patients

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with advanced and otherwise hopeless cancer. Much new knowledge has recently been obtained by finding those tumors that are estrogen binding or estrogen sensitive, but the procedure still has its limitations and this we must recognize.[24]

In patients with advanced cancer who were beyond menopause, Nathanson and Aub found that the administration of estrogen oftentimes caused prompt reversal of growth of the tumor, a reprieve often for as long as two years.[26] They also found that androgens given to a patient before menopause or after an initial run on estrogen might bring a secondary reprieve.

Aub was not alone in his interest in the endocrines. Lacassagne in France had also found that estrogens were important in breast cancer.[21] He was able to produce breast cancer in mice by administering the newly disclosed synthetic estrogen.

Then in Chicago there was Charles Huggins, another endocrine genius like Aub. Professor of urology at the University of Chicago, he was interested, of course, in subduing prostatic cancer. He also tried orchidectomy and found its effect limited.

He realized that orchidectomy might be failing because of the secondary source of androgens in the adrenal cortex. Accordingly he undertook bilateral adrenalectomy to reduce the level of androgens and to supplement the initial orchidectomy.[19] The adrenalectomy was a perilous operation at that time (1941) because of the lack of significant adrenal cortical support; but he could see that the adrenalectomy had an influence. Later when cortisone became available to support the patient metabolically, Huggins recorded the beneficial effect of combined orchidectomy and bilateral adrenalectomy. The operations, of course, helped but again, like the observations of estrogens in patients with breast cancer, the beneficial effect was limited and transient.

In retrospect it should occasion no surprise that the efforts of Aub, Huggins, their colleagues and many others should have proven ineffective, unable to eradicate cancers of the breast and prostate. Endocrine hormones are kindly, productive, physiologic substances. Cancers are vicious tumors and need vicious opponents to subdue them. Even though only partially effective, ovariectomy, orchidectomy, hypophysectomy, and adrenalectomy have been a help to a great many people suffering from the endocrine influenceable cancers and still these surgical maneuvers may help when all else has failed. In those patients whose tumors are hormone sensitive, a significant respite can be obtained, giving them comfort and some freedom of life. They are not to be degraded or abandoned at this juncture. It has been an interesting, historic contribution of endocrinology to the control of cancer of the breast and prostate.

GOITER

A different view of the history of endocrine surgery is obtained from the care of goiter. The first treatment was surgical and the first objective was to remove the goiter because of its mechanical pressure and unsightly presence. During the course of the early surgical endeavors much of the thyroid's endocrine function was disclosed. It was the surgeon who discovered the nature of the tumors contained in the goiter and the need for the control of over- and under-production of the hormone. Here is the story.

Goiter, in a visual sense, is an external trouble obvious to everybody, and since earliest recorded time it has been a common curse in iodine deficient lands. It is not surprising therefore that goiter was the first endocrine disorder to be tackled surgically. Excisions of goiters were attempted many hundreds of years ago but not until the arrival of modern surgery in the second half of the 19th century with anesthesia and asepsis could surgeons achieve progress in the control of hemorrhage, suffocation and cardiac failure. Throughout the West many surgeons strove to acquire adequate techniques. Years of effort were needed. So important was progress considered that Kocher of Bern, Switzerland, was awarded the Nobel Prize for his achievement in thyroid surgery in 1909.[20] He was the first and only surgeon for many years ever to receive this award. Surgical success gained well deserved appreciation, and clinics in the United States such as those of the Mayo brothers and of Lahey were established in no small part on the reputation gained in their management of goiter.

Of particular note were the several achievements of Halsted between 1880 and 1910. The first professor of surgery at the Johns Hopkins Medical School, he made many original observations in regard to the thyroid.[16] In experiments on dogs he described the compensatory hyperplasia of the thyroid gland after its subtotal resection. He studied the pathology of goiter. He described the intimate vascular anatomy and was the first to develop a virtually bloodless technique. Of all surgeons, here and abroad, he contributed the most to thyroid surgery.[16]

The management of nontoxic goiter was one thing, that of hyperthyroidism another. Now in 1978, three generations later, it is wise to remind ourselves that the initial surgical successes were with patients who had nontoxic nodular goiters. Surgeons had learned to be wary of patients with exophthalmic goiter (Basedow's disease). In no small measure it was the surgeon who called attention to the patient with toxic nodular goiter, the form of thyrotoxicosis without the obvious eye signs. The high metabolic rate with its demand for oxygen, the increased cardiac output, the rapid bounding heartbeat, and the extraordinary hypersensitivity to adrenalin made both groups of toxic patients high risks for operations. In the presence of the excessive hormone many patients died on the operating table or soon after. The need for better understanding was apparent to all.

When I was a first year student at medical school (1923), Dr. Lahey told us how he had divided the operation on thyrotoxic patients into 16 steps; at any step he could stop the procedure to give the patient a rest. If the patient was reacting poorly when he or she arrived in the operating room, he sent the patient back to the room; that was the first step. If, as he started the operation, the pulse rate rose precipitously, he closed the operative field, returning the patient to his bed, to resume the operation at a later date when the patient's state was quieter.

One of Lahey's initial operative steps was the ligation of the four major arteries, a measure earlier recommended by Halsted. An abrupt fall in metabolic rate followed. At a second procedure one lobe might be resected and at a third, the second lobe. Such maneuvers circumvented the often disastrous mortality of the earlier years and Lahey became famous.

In other parts of the world the surgical mortality in patients with toxic goiter was so ominous that not infrequently internists refused to refer patients to the surgeon. Supportive measures and waiting out the disease were tried instead. In 1926 I had the good fortune of serving as a student clerk on the medical wards in Munich, Germany, under Professor Friedrich von Müller. The medical assistants and students of the time referred to the surgeon who managed the surgical service parallel to Professor von Müller's medical service as "The Butcher," his mortality with toxic patients was so high. Professor Müller refused to refer patients to the surgical service and advised them to go to the Bavarian Alps and to stay there for two years. He pointed out that after this prolonged stay in the mountains they returned to Munich rid of their disease.

I had not the wit then unfortunately to realize what was happening to the patients in the Bavarian Alps. It was the very same area where people were developing the goiter of iodine deficiency. Professor Müller was depriving his thyrotoxic patients of iodine and of course their thyrotoxicosis improved. Their glands had no iodine with which to manufacture the excessive thyroid hormone and the effect was the exact equivalent of Astwood's introduction of the antithyroid drugs which chemically deprives the thyroid gland of iodine (1943).[3]

The introduction of iodine in the United States in 1916 in the prevention of iodine deficient goiters had not as yet been appreciated by Europe. Though iodine had been tried by some physicians, the occurrence of iodine toxicity in patients with established goiters had alarmed them and the general introduction of iodine was delayed for some years. Europe's initial avoidance of iodine and America's inattention to what happened to a patient with toxic goiter when sent to an iodine deficient area were the results of poor communication between doctors, the failure to appreciate what others were contributing.

But surgical maneuvers such as those of Lahey were enormously time consuming and costly to patient and hospital. The avoidance of the operation with the two year stay in the iodine-deficient Alps was also costly and available to but a few patients. Surgery needed more effective support.

The first help came in 1923 when Plummer, a physician at the Mayo Clinic, introduced iodine in the preoperative preparation of the thyrotoxic patient.[28] The

iodine induced a prompt remission in hyperthyroidism but its effect was only partial and often not sustained. Partial though it was, for the first time medical control of hyperthyroidism became a reality. Because the iodine effect was only partial, surgical subtotal resection of the goiter was still needed to bring the metabolic rate to normal. The remission induced by iodine, however, permitted a less hurried, more careful surgical excision. The mortality of the operation was sharply reduced and success became predictable. For the 15 year period from 1926 to 1941 surgery after iodine preparation held sway in the management of hyperthyroidism. The success was a triumph.

The next phase, the third, in the management of Graves' disease, the first real challenge to surgery, came in 1941 with the introduction of radioactive iodine by Means, Evans and Hertz.[18] Its use is now standard and ^{131}I therapy has largely replaced surgery.

The fourth phase of treatment of hyperthyroidism, that with antithyroid drugs, came two years after the introduction of radioiodine. In 1943 Astwood introduced thiouracil, a drug which interfered with the iodination of thyroxin.[3] The level of thyroid hormone production for the first time could be truly regulated medically. At this point the treatment of hyperthyroidism in principal passed from surgical to medical. Although in many areas surgical subtotal thyroidectomy has continued to be used, particularly in younger people, theoretically surgery is no longer used in the care of thyrotoxicosis.

The fifth phase in the treatment of exophthalmic goiter stemmed from a chance conversation in 1944. I was having lunch with Dr. Stanley Cobb, my teacher of neuropathology who in 1934 had moved from Chief of Neurology at the Boston City Hospital to direct the new department of psychiatry at the Massachusetts General Hospital. We were discussing acute grief when he abruptly changed the subject saying, "by the way, Oliver, it is high time that you people in the thyroid clinic paid attention to what we psychiatrists know about the genesis of exophthalmic goiter." Of course, I listened carefully. I knew that Graves in his original description of exophthalmic goiter had recounted that one of the first four patients had had an emotional upset prior to the development of the goiter and that he had suggested that the upset was perhaps responsible. I knew then as I still know today that almost all physicians have abandoned this notion of Graves, and have come to believe that the emotional troubles encountered by patients with exophthalmic goiter are the result and not the cause of the hyperthyroidism.

Because of the poke given me by Dr. Cobb I began looking more closely at patients with acute Graves' disease, questioning them about their lives before and at the time of the onset of the disease. Coached by Cobb and other members of our department of psychiatry, I began to hear and see things. Then too I knew of Wislocki's description of the portal-hypophysial circulation carrying venous blood from the hypothalamus to the pituitary[37] and of the studies of Penfield into the limbic system of the brain.[27] (Cobb and Penfield were close friends and colleagues in the study of neurology.) Little by little it became evident, just as Cobb had told me, that the majority of patients with Graves' disease had had emotional troubles before the development of goiter and exophthalmos. The concept that emerged was that the emotional troubles centered in the limbic system which sent alarm signals to the hypothalamus which in turn directed the anterior pituitary to increase the stimulation of the thyroid. By the late 1950's it had obviously become time to test this concept in therapy, not hold it as a theoretical concept.

In 1958 the first patient was chosen for a trial of psychotherapy as the primary treatment for Graves' disease. Prior knowledge of disturbance of this patient's ovarian function in response to an emotional problem made her a suitable patient for the initial trial. The prompt early response to psychotherapy was striking to both the patient and her doctors. I have described her troubles and the course of her Graves' disease in the prologue to Man, Mind and Medicine.[10] At that time the steps from the amygdala of the limbic system to the hypothalamus and then by the portal hypophysial circulation to the anterior pituitary had only been described as possibilities, and the thyroid releasing hormone of the hypothalamus, although predicted, had not been identified.[22]

Since 1958 the psychotherapeutic approach has been tried in 85 patients. From the beginning Dr. Farahe Maloof, Chief of the Thyroid Clinic, and I have shared in

Table 1. *Primary Psychotherapy in Hyperthyroidism*

OUTCOME	NO. OF PATIENTS
Graves' Disease	
Success	18
Partial success	14
Failure with psychotherapy	10
Failure to initiate psychotherapy	12
Initial thyroid therapy, delayed psychotherapy	21
Subclinical Graves' Disease	10
TOTAL	85

the care of the patients. There have been signal successes, moderate successes and failures (Table 1).

Failures are included in our accounting because the histories which the patients gave us indicated that had they or their physicians been willing that psychotherapy be undertaken, much could probably have been achieved. Some at least could have met with success.

At present writing there seems no doubt that in most patients with Graves' disease, an emotional disturbance involving the limbic system is the primary difficulty. Both the eyes and the goiter are motivated through a complicated system involving the central nervous system and hormone releases. In essence the eyes and the goiter are separate end organs of action of disease primarily in the limbic system.

If this proves true, and Dr. Maloof and I and our colleagues believe that it will, then the whole order of the treatment of patients with Graves' disease will come full swing from local surgical care of the goiter, through radioactive iodine and antithyroid drugs to therapy directed at control of the limbic system in the central nervous system. Surgery will presumably be less and less used. Radioactive iodine likewise should rarely be needed. Antithyroid drugs will continue to be useful in reducing the thyroid activity to normal to make the psychological readjustment easier. How the initial troubles in the eye can be alleviated is not yet understood as that mechanism from the cerebral cortex to the eye is still not understood. Much evidence indicates that it is in its final outlet different from that leading through the pituitary to the thyroid gland.

Many physicians and surgeons who care for patients with Graves' disease will remain skeptical of primary psychotherapy. But I would remind them that for many years we have used exactly the same approach in treating many women who have had ovarian dysfunction due to emotional trauma. Such psychotherapy is so common that we forget about it. Let me give you some examples.

OVARIAN DYSFUNCTION

Almost every woman sometime in her life has had the experience of missing one or more periods following some form of emotional upset. The upset can be the turmoil of moving house, or the sickness of a child, or the death of a loved one. Such a derangement of ovarian function should occasion no surprise and no doubt in the mind of the physician of how it is best treated.

The beneficial effect of adopting a child upon the fertility of a previously infertile couple is another example. A couple that has been unable to achieve a pregnancy from 4 to 8 years finally decide upon adoption. Although it is disputed by some statisticians, so frequently is the adoption followed by a pregnancy that it stands to reason that the decision regarding adoption may bring such repose that ovulation is achieved and pregnancy occurs. Of course, adoption will not always

succeed in pregnancy. There are other causes of infertility but lack of statistic significance fades in the face of common experience.

ADRENAL CORTEX AND CUSHING'S DISEASE

Much of what has just been said about the thyroid gland and exophthalmic goiter can now be said about the adrenal cortex and Cushing's disease.

ACROMEGALY

I have had little responsible contact with patients with acromegaly but Richard Rovit tells me that acromegaly also seems to be a psychosomatically induced disorder comparable to patients with exophthalmic goiter.[30] If so, then subtotal surgical removal of the pituitary or irradiation of the pituitary would be a much less advantageous treatment than primary therapy of the limbic system disorder. The pituitary has too many functions important to life of both male and female to reduce indiscriminately any or all of them. In general, the nearer the therapy to the origin of the disease, the better the therapy and the fewer the recurrences.

PARATHYROID

After the close of World War I Joseph Aub was put in charge of Harvard's study of lead poisoning. He and his colleagues found that lead followed calcium in and out of bones, that lead colic could be quickly controlled by calcium intravenously, and that a high calcium intake carried lead along with the calcium into the bones. In reverse, when a patient with lead in the bones was placed on a low calcium diet, the calcium and lead were recalled from the bones; if this recall proceeded too rapidly, lead colic was once again induced. He further found that the withdrawal of lead from the bones could be expedited by parathormone.[1] It was this last discovery, reported in May 1925, which led the following winter to identification of hyperparathyroidism in the famous sea captain, Captain Martell. The metabolic findings in Captain Martell, the elevated serum calcium, low serum phosphorus, increased excretion of calcium in the urine, and decreased excretion in the feces were exactly those obtained in the patient with lead poisoning given parathormone. Together with Dr. DuBois of New York, Aub and their colleagues reported these observations as the first diagnosis of hyperparathyroidism.[1, 5, 17] Their findings and the initial operations on Captain Martell took place before the published report from Vienna, where Felix Mandl had diagnosed hyperparathyroidism in 1925 on the basis of reversing a pathologic dictum.

In Europe the bone disease, osteitis fibrosa cystica generalisata had been described in 1891 by von Recklinghausen in Strassburg.[34] In 1904 Askanazy, the pathologist at Kiel, found an enlarged parathyroid, presumably an adenoma in a patient dying of that bone disease.[2] During this same period the famous pathologist, Erdheim of Vienna, had been much interested in the parathyroid gland. He had found them enlarged in rats deprived of vitamin D and he concluded that the enlarged parathyroid in Mandl's case was secondary to the bone disease, not its cause.[15] Such was the respect for Erdheim's opinion that his conclusion was accepted until 1918 when Schlagenhaufer suggested that perhaps it was the other way around, parathyroid enlargement the cause, not the consequence.[32]

Dr. Mandl, a surgeon in Vienna, was the first to put this question to test.[23] In the summer of 1925 a patient appeared on the surgical service of Dr. Mandl suffering from osteitis fibrosa cystica generalisata. Dr. Mandl argued that if Erdheim was right, then a graft of parathyroid tissue to the patient should bring improvement. This he tried but it did not affect the well-being of the patient. He therefore decided to try the reverse, the suggestion of Dr. Schlagenhaufer. He explored the neck of the patient and found an enlarged parathyroid. He removed it and the patient improved.

Dr. Mandl reported this experience before the Vienna Medical Society at Christmas time in 1935. The report was not distributed until after Dr. Aub's study and the initial operations of Dr. E. P. Richardson to find an abnormal parathyroid.[29]

After a short period of improvement, Dr. Mandl's patient grew worse. Dr. Mandl operated upon him again but failed to find any further parathyroid tissue. Subsequently the patient died, presumably of hyperparathyroidism. At autopsy no further parathyroids were identified.*

To return to Dr. Aub in Boston, Aub had arrived at the diagnosis of hyperparathyroidism by metabolic study. In Vienna the diagnosis had been established by denying the traditional concept of the pathologists. The differences of approach in making the diagnosis in the two cities, Boston and Vienna, had far reaching consequences. In Europe for many years, hyperparathyroidism remained a disease of the bones. In the United States, as the result of continued metabolic study, it was realized that the bone was only one of the complications of an excessive concentration of parathyroid hormone.

The manner in which hyperparathyroidism was discovered in Boston compared with Vienna is instructive. Vienna was well aware of what the pathology of the parathyroid might be, not so in Boston. Boston's thyroid expert who undertook the operation in April, 1926, and the second operation six weeks later in June, had an inadequate image of where parathyroids were to be found and what they looked like. At the first operation, he explored the right side of the neck and found a parathyroid; it looked large and he took it out. The removal had no effect. At the second operation he explored the left side of the neck and again he found what looked like a possible enlarged parathyroid. He removed it and again there was no change. Surgeons of that time had little idea where to look or what to look for. They thought of the parathyroids as glands to avoid at all cost and best not to see them during the removal of a goiter. How else could they avoid injuring them?

The pathologists of the time also did not know the intimate anatomy and pathology of the parathyroid. In 1931 when I was advised by Dr. Churchill to go to the pathology laboratory to carry out parathyroid dissections at autopsy, the Assistant Pathologist and I competed to see who could first learn with certainty what was parathyroid, what was lymph node or fat. It was the surgical need that forced me to do the dissections, to learn the normal distribution of the parathyroids, where they might hide, and what they looked like, normal and abnormal.

On the basis of present understanding, control of the parathyroid gland appears to involve a different mechanism than that of the limbic hypothalamus-anterior pituitary system. Clinical studies of patients with hyperparathyroidism have thus far failed to reveal any preexisting emotional disturbance. In contrast to hyperthyroidism, the emotional disturbance that accompanies an elevated calcium level is promptly and apparently fully relieved by surgical correction of the parathyroid hyperfunction.

Thus far, no hormonal-like substance has been identified secreted in the brain stimulating the parathyroid glands. (The kidney is a possible source in view of the secondary parathyroid hyperplasia encountered in chronic renal disease.) Yet a stimulating, balancing system must exist. Excessive removal of the parathyroid glands with consequent hypoparathyroidism and a low calcium, high phosphorus level results in prompt compensatory hyperplasia of a parathyroid remnant and relief of the hypoparathyroidism. The sensitivity of the nervous system with the transmission of the neuromuscular impulse so acutely sensitive to the calcium level, it would seem reasonable to suppose that the controlling factor involved in parathyroid function must lie somewhere in the central nervous system. Yet such an area, or areas, has not been identified.

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*At his initial operation Dr. Mandl queried whether the large parathyroid he had found was hypertrophic or adenomatous. The pathologist, after study, concluded that it was an adenoma. It is remarkable that Mandl, the surgeon, should have questioned the identity of the enlargement. The published reproductions of the microphotographs suggest that the tumor resected in 1925 was chief cell hyperplasia. In view of the recurrence of the metabolic hyperparathyroidism, it is likely that had the pathologist been more knowledgeable about the gross anatomy of the parathyroids, he might well have found three additional enlarged hyperplastic parathyroids at autopsy.

Several problems in clinical management of patients with hyperparathyroidism await elucidation of the physiologic mechanism of parathyroid control. This need for knowledge is particularly evident in the present dispute over how parathyroid hyperplasia should be managed.[9, 35]

The discussion thus far has centered on aspects of hyperfunction. Space does not permit comparable consideration of other glands, for example, the pancreas, pheochromocytoma, and that disease of still uncertain origin, myasthenia gravis. I shall close with a brief account of the surgeon's contribution to the anatomic pathology of the endocrine system.

Ever since 1900 surgeons and pathologists have disagreed regarding the distinction between hyperfunctioning hyperplasias and neoplasias. Is hyperplasia a necessary forerunner of hypersecreting neoplasia? Are the nodules of hypersecreting glands just conglomerations of hyperplastic cells or are they true neoplasms, benign or malignant? What does the surgeon need to remove—the lumps or the internodular tissue?

The disagreement arose first in the lumpy goiters of patients with hyperthyroidism. In the Middle West where iodine deficiency goiters were abundant, the goiters were called adenomatous. Pathologists in the East argued that the lumps were not proven adenomas and that the descriptive term nodular goiter was to be preferred. Adenoma should be reserved, they thought, for a group of cells growing independently of the rest of the gland, a benign neoplasm. If the lumps were adenomas growing and hyperfunctioning independently all within one gland, then the thyroid must indeed be a most unusual gland.

The issue became important in the early 1930's as the need to understand the surgical pathology of hyperparathyroidism became apparent. Initially this disorder was believed due to adenomas, certainly one, perhaps two or even three. Dr. Churchill and I got taken in on this. In our first 50 cases of hyperparathyroidism, 15 cases were classified by surgeon and pathologist as due to multiple adenomas. This seemed unrealistic; more information was needed. A new look at the thyroid provided the clue.

In the course of operating upon patients with thyrotoxicosis in the 1930's, I encountered 10 patients with a single large nodule and obvious atrophy of the opposite lobe including the rest of the lobe in which the nodule lay.[14] These patients were seen before the advent of radioactive iodine so that useful measure of function was not available. Instead the atrophy of the non-nodular tissue provided a physiologic explanation. The nodule must be the source of the excess hormone and the excess must have suppressed the activity of the non-nodular tissue resulting in the atrophy. Thus the lump fulfilled the criteria of an independently secreting adenoma. A look at the adrenals of patients with Cushing's disease revealed the same pair of findings. If the surgeon found atrophy, gross atrophy, of one adrenal cortex, a single hyperfunctioning neoplasm, an adenoma or carcinoma, was certain to be found on the other side.[13]

Returning to the parathyroids, in the first years of experience with hyperparathyroidism at M.G.H (1926–1935) we had the same impression. When one gland was enlarged the other 3 or 4 were atrophic, smaller, and yellower than normal. Again the enlargement was a hyperfunctioning adenoma, the others were atrophic from lack of stimulation, an atrophy of disuse.

But how were we to explain two enlarged parathyroids? In such cases, as we looked at the other 2 or 3 parathyroids, they were not fatty and atrophic but enlarged apparently by the same cellular process. Obviously the physiologic diagnosis must be diffuse hyperplasia, a type comparable to toxic nodular goiter, not multiple independent hypersecreting adenomas.

Looking back at the hypersecreting tumors of the thyroid and adrenal cortex, we soon realized that not one case associated with atrophy of the uninvolved nontumorous tissue was associated with two adenomas, or two carcinomas. If multiple secreting neoplasms, either adenomas or carcinomas, ever occur in the thyroid, adrenal cortices, or parathyroids, they must be a rarity. If the lumps are multiple then they are the nodules that build up in hyperplastic glands, not true neoplasms. The more we surgeons looked the more certain we became that this is a generalization—a surgical, pathologic rule—the presence of atrophy means the hypersecretion is stemming from a physiologically independent mass of cells, an

adenoma or carcinoma, and that there is but one such hypersecreting mass. It took us some time to convince the anatomically minded pathologists that there was no such entity as double hypersecreting adenomas.[12] To the physiologically minded surgeon, the rule was salient because if atrophy is found in one area, any enlargement found elsewhere must be the independent hypersecreting neoplasm which is to be removed. Having found one, the surgeon does not need to search further.

This generalization or rule appears to stand today. It has been observed in three separate gland systems, the thyroid, adrenal cortices, and parathyroids. It is an example of a contribution of the endocrine surgeon to the pathology of endocrinology. Finally, it appears likely that it is such a biological feat to make one hyperfunctioning adenoma (or carcinoma) that a coincidental second hypersecreting neoplasm is highly unlikely.

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Some Post-Hunterian Schools of Surgery

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Several well known leaders among British surgeons indicated to this surgeon in the summer of 1967 that it was their belief that the surgical residency scheme of training had originated with Halsted at The Hopkins. in 1904, Halsted wrote a magnificent address on The Training of the Surgeon in which he indicated that the length of the training period at The Hopkins was then eight years beyond the internship.[10] However, Halsted said his plan was modeled after the German scheme of Langenbeck and Billroth.

The earliest and most durable influence upon American surgery was distinctly British. Primarily, John Bell of Edinburgh and John Hunter and Astley Cooper of London provided instruction for early American surgeons who went abroad for study.

At a somewhat later date the Paris School of Surgery of Pierre Desault represented by Larrey, Lisfranc, and Dupuytren and their intellectual descendants, Velpeau and Nélaton, inspired American surgeons. Contemporaneous with the origins of the Desault School (1785) there developed in Vienna under Emperor Joseph II a military school of surgeons under the successive leadership of Brambilla and v. Kern that endured up until the time of Billroth. And at a still later date, successively K. v. Graefe, Dieffenbach, and Langenbeck of Berlin, and the latter's brilliant pupil, Billroth, who held professoriates in Zürich and Vienna, and their intellectual and professional progeny were the primary source of stimulation and instruction for American surgeons.

John Bell of Edinburgh (1763-1820) was the elder brother of Charles Bell, the more distinguished surgeon-physiologist. However, John Bell was a superb teacher to whom both Philip Syng Physick and Ephraim McDowell were exposed. John Bell's 1809 monograph on the Education of the Surgeon is well worth reading today.[1] McDowell, in the pioneer hinterland of Kentucky, first sent his manuscript on ovariotomy to Physick; when no word reached its author, McDowell sent his paper to John Bell, who was ill and on a holiday in Italy. His nephew, William McDowell, took a copy of the manuscript to the Professor of Obstetrics and Gynecology, Thomas C. James at the University of Pennsylvania, who read it to his class and submitted it for publication. It appeared in print in 1817.[17]

Physick, in the early 1790's, after having spent a year as house-officer at St. George's Hospital in London under the tutelage of John Hunter, went to Edinburgh and audited the lectures of Alexander Monro II. Later, Physick implemented Monro's suggestion of employing extensive phlebotomy for chronic dislocation of large joints, a method which Physick used with great success, withdrawing from such patients as much as two liters of blood; with the patient in the standing position, bleeding was performed on both veins of the forearms simultaneously. The sudden great loss of blood volume occasioned the patients to sink to the floor in syncope. The phlebotomy provided not only analgesia but complete loss of muscle tonus not achievable by deep ether anesthesia, unless complemented by infiltration of procaine in the area to prevent centripetal spread of painful stimuli.[24] Crile (1913)

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achieved this state of muscle relaxation with a combination of inhalation anesthesia (ether) and local procaine injections, which procedure Crile called anoci-association.[4]

John Hunter (1728–1793), essentially self-trained save for a period of tutelage under the direction of his elder brother William Hunter, became one of the leading surgeons of his time. He was essentially a surgical thinker and the creator of experimental surgery and pathology. Hunter was not a great lecturer; nor was he a talented operating surgeon. His forte was essentially communicating in dialogue with some of his house-officers and those enjoying back stair privileges at his home. He had an unusual perceptive skill in recognizing talented young persons with whom he spent considerable time in long evening sessions in his home, addressing to them a succession of questions in dialogue. Undoubtedly, Hunter's unusual method of instruction brought out the finest talent in many a young mind. This Socratic method is still the hallmark of the success of many a modern day talented surgical leader, whether in seminar, conference, or in tete a tete conversations, and discussion; the latter was Hunter's preferred method.[24]

John Abernethy, one of John Hunter's pupils, was said by D'Arcy Power to have been one of Britain's finest undergraduate surgical teachers. Said Power, Abernethy made every student in his large class feel their lecturer was the finest teacher in the world and that each student was only a notch lower.[20] This type of encouragement undoubtedly was the source of great stimulation to many of his auditors. John Hunter's pupil, Astley Cooper, also left a school of surgeons of great talent. Cooper was primarily a talented operating surgeon with a flair for experimentation, the author of many books, and a brilliant undergraduate lecturer. However, both Abernethy and Cooper lacked the skill and the ability to stimulate their surgical pupils to serious and original thought as did Hunter.

The Desault School

Ambroise Paré (1510–1590) spent three years as house-officer at Hôtel-Dieu (1533–1536) but failed to mention any of his teachers by name. In fact, whereas France had many distinguished surgeons in the persons of Lanfranci (d. 1315), often called the father of French surgery, and his loyal pupil, Henri d'Mondeville (1260–1320), and Guy de Chauliac (1300–1368) of Avignon, Hôtel-Dieu could not boast of any distinguished or accomplished surgeons until the arrival of Pierre Desault at the Hôtel-Dieu of Paris in 1785.[3] There, in a few short years, Desault developed an impressive school of surgeons, trained in surgical anatomy and the performance of operations representing the finest Paris surgeons of that day: among others, Chopart, Percy, Bichat, Dominique, Larrey, and Dupuytren, all of whom received their primary stimulus to pursue surgery as a career from the teachings of Desault. His influence continued through his pupils to a second generation of French surgeons amongst whom can be enumerated Roux, Lisfranc, Velpeau, Malgaigne, and Nélaton. In fact, the physicians Corvisart and Broussais, and the pathologist Cruveilhier, drew their stimulus also from the Desault surgical school.

Origins of the Vienna Military Surgical Academy

Maria Theresa, Empress of Austria and Hungary, invited van Swieten (1794), a pupil of Boerhaave of Leyden, to head the University of Vienna's department of medicine. Her son Joseph II selected the Italian surgeon Brambilla to come to Vienna (1785) to inaugurate a military surgical academy, independent of the University, to train surgeons for the Austrian army. With the approval of the Prince, later the Emperor, the School was authorized to award degrees. Brambilla retired in 1795 and died in Italy in 1800. Yet, the School continued to thrive despite periodic interruptions. Located first at Gumpendorf, the Academy later moved to Vienna on Währingerstrasze where the Medical Historical Institute today resides near the midst of the medical campus. Johann Hunczkovsky (1752–1798), with strong training in France and England, was one of the Academy's first great surgeons. Under the direction of a succession of able leaders, it developed a strong faculty. Carl Ludwig, the celebrated German physiologist was there for ten years (1855–1865). The illustrious biochemist, Willy Kühne, was there for a shorter period, as were Toldt, Kupffer, and Métz in anatomy; and Weichselbaum, Müller, and v. Reckling-

hausen in pathology. These medical scientists added status to the military academy that succeeded in training a large number of physicians and surgeons who became professors in several medical schools. The Josephinum, the Military Academy established by Joseph II, was closed permanently in 1874.*

At a later date, Vincenz v. Kern (1760–1829) developed under the auspices of the University, the Operateur Institut,[23] with a commitment to train surgeons for military service, while functioning simultaneously as a university surgical clinic. Billroth (1867) was the first professor of surgery at the University of Vienna, coming directly from a Zürich professoriate, who did not have his primary training in the Operateur Institut. A few years later as surgical antisepsis and elective surgery loomed on the surgical horizon, Billroth abolished the v. Kern school of practical surgery and supplanted it with surgical assistantships, with young surgeons living in the hospital to carry out preoperative studies and supervise the postoperative care of surgical patients.

The Hunter, Desault, and v. Kern schools of surgery antedated the arrival of two great nineteenth century innovations, anesthesia and prophylactic surgical antisepsis. The Langenbeck-Billroth schools emerged while antisepsis was in the making.

Significant Nineteenth Century Innovations

Anesthesia and prophylactic surgical antisepsis were products of the mid-nineteeth century and constituted two of the most sorely needed and finest surgical therapeutic endeavors of any period. These two innovations came from two Cinderellas of the profession. The dental surgeons W. T. G. Morton (1846) and Horace Wells (1844) provided inhalation anesthesia. From experiences with ether frolics, Crawford Long of Jefferson, Georgia instituted use of ether for operative procedures early in 1842,[15] four and one-half years before the public demonstration of ether by Morton on 16 October, 1846 at the Massachusetts General Hospital. Elective surgery came only with acceptance of microbiology and the germ theory of disease in the 1876–1886 period, probably the most welcomed therapeutic contribution to medicine and surgery of any period in time.

The nature of contagion had its birth pangs with Hieronymus Fracastoro (1546), a contemporary of Ambroise Paré and Andreas Vesalius, who emphasized the role of direct contact with *seminaria* (germs) in the communication of infection.[5] Leeuwenhoek described bacteria in the final decade of the seventeenth century; it remained, however, for Robert Koch (1876–1878) to establish definitely the pathogenicity of bacteria,[12] to which the work of Theodor Schwann (1837), Jacob Henle (1840), Louis Pasteur (1860–63), and Joseph Lister (1867) also had made significant contributions. Actually Ignacz Semmelweis had definitely shown and proved (1847–1861) the manner of conveyance of puerperal fever by carefully devised studies at the Allgemeines Krankenhaus in Vienna in the pre-microbiological era,[22] leading to a sharp reduction in maternal mortality throughout Austria and Germany by 1864. The innovation of diagnostic radiology by Wilhelm Roentgen (1895) was for greater medicine a unique and significant contribution.[21] William H. Welch (1913) indicated it was his belief that the creation of the Surgeon-General's Catalogue and Index Medicus by John Shaw Billings (1880) was an innovation paralleling in importance the introduction of ether anesthesia.[25]

Important Twentieth Century Innovations

Insulin (1922), cortisone (1934), sulfanilamide (1935), penicillin (1942–1944), and vitamin B_{12} (1948) have proved to be miraculous therapeutic agents of this century. Conquest of tuberculosis, the leading cause of death in the United States at the beginning of this century, was initiated by elimination of bovine tuberculosis by the Live-Stock Sanitary Board in America (1910–35); followed by pasteurization of milk; the serious threat of human tuberculosis has been virtually eliminated in

*Theodor Puschmann, the Viennese Medical Historian (1889) wrote A History of Medical Education in which he described the Josephinum Military Academy, and the Operateur Institut at the University of Vienna. (Translation by E. H. Hare, London, H. K. Lewis, 1891; facsimile London, Hafner, 1966, pp. 565–572.)

countries of Western culture through streptomycin (1944) and other effective antibacterial agents. The important role of orthopedic, general, and thoracic surgeons in the management of tuberculosis of bones and joints, tuberculous lymph nodes, and pulmonary tuberculosis, respectively, has been set aside. Conquest of poliomyelitis came about through the discovery of Enders (1949) of cultivating the polio virus, and the practical vaccination programs of Salk (1953) and Sabin (1955), an accomplishment the whole world recognizes as a great victory for medicine, eliminating the threat of this dreadful killer and creator of severe paralytic deformities; in consequence the activity of correcting such deformities by orthopedic surgeons has been guided into other channels.

The most significant surgical innovation in the twentieth century was development of intracardiac surgery to which the pioneer work of John Gibbon of Philadelphia in the mid-1930's by creation of a pump oxygenator to substitute for the heart and lungs during cardiac standstill created the initial stimulus.[7] F. John Lewis of the University of Minnesota in September 1952 had the first success in man with open heart surgery, closing an interatrial septal defect in a girl of seven years under systemic hypothermia.[14] The training of a number of talented and skillful young surgeons in the knowledge of physiology of the circulation under the tutelage of Maurice Visscher, a pupil of Ernest Starling, accounted for the circumstance that a large number of Minnesota trained surgeons came to play a significant role in the development of intracardiac surgery, concerned first with correction of congenital cardiac defects, followed by operations for acquired valvular lesions.[8] C. Walton Lillehei emerged as the Leader of this great band, constituted by Clarence Dennis, Richard Varco, Morley Cohen, Herbert Warden, Richard DeWall, Vincent Gott, Norman Shumway, Christiaan Barnard, Aldo Castaneda, and others. This program, begun after World War II, came to fruition in the mid-1950's, in which achievement this surgeon was only the water-boy and sideline cheerleader.

The first significant contribution to emerge from intimate working relationships between the departments of physiology and surgery at Minnesota, an arrangement that existed from 1936 to the superannuation of its principals, was the mass spectrograph for the guidance of anesthesiologists during administration of inhalation anesthesia. In the late 1940's and early 1950's, it was common practice to give several inhalation anesthetic gases concomitantly. Unfortunately, anesthesiologists had no way of knowing the respective concentration of the gases administered. Visscher and I took the problem to Alfred Nier, eminent Minnesota physicist who had built a mass spectrograph for instantaneous assessment of various gases. In fact, Nier kindly provided us with one of his early models, which was immediately put to good use in the hands of our surgeons Fletcher Miller and Richard Varco.[18] Our anesthesiologists quickly found it an extremely useful instrument; today it is universally applied in the form of a small compact portable device. The Nier spectrograph is employed today in determination of the chemical content of the soil on Mars relayed from a guided satellite and deposited there. Nier's early work with the mass spectrograph antedated the work of John Bardeen and his colleagues of the Bell Telephone Company, awarded the Nobel Prize for invention of the transistor in 1948.

Research Center Approach

In the solution of difficult and stagnant problems the research center approach has become standard procedure. Transplantation, which occupies the attention currently of a large number of talented surgeons throughout the world, employs the skill, talent, and knowledge of the finest representatives of a number of disciplines including biology, botany, experimental pathology, genetics, microbiology, pharmacology, physiology, and zoology. When the rejection phenomenon attending transplantation of allograft organs whether heart, liver, kidney, or skin is overcome, surgery will have taken another tremendous stride forward. What discipline will provide the needed answers for that achievement remains an enigma.

There are, however, periods of Lull between significant discoveries. Medical advance is essentially a discontinuous process often marked by relatively long periods of standstill. By accumulating all the available existing evidence bearing upon an issue, considerable progress nevertheless can be made. Witness what

obstetricians have achieved in the past few decades with cesarean section. At the turn of the century, the operation was undertaken primarily only after parturients had been in labor for several days, and segments of uterine mucosa had already undergone necrosis; performance of cesarean section at that juncture was consistently followed by a mortality varying from 40 to 60 per cent. By simply instituting cesarean section before labor sets in for parturients in whom the intrauterine fetal position portends long labor, the mortality has been reduced to zero in many large series enumerating patients by thousands.[24] It obviously is a technique that can be applied to many illnesses. McBurney (1889) postulated that with early surgical intervention for appendicitis, the mortality could be reduced to zero.[16] It continued an important cause of death in this country up until the mid-1930's. Tables of Vital Statistics reveal that 1066 patients (1973) within the borders of the United States died from rupture or gangrene of the appendix. Voluntary cooperation of groups elucidating and publishing the causes of maternal mortality of parturients in labor by the New England obstetricians under the leadership of Jewett has alerted the profession and the public to neglect, and errors in professional judgment, causing death of patients. It obviously is a mode of learning that could be used to the profession's advantage in many ills, including appendicitis.

The Surgical Hospital Residency Is French in Origin

Allusion has already been made to the circumstance that Ambroise Paré enjoyed a period of hospital training at Hôtel-Dieu in Paris in the years 1533–1536. Corlieu (1897) related that by 1642 the scheme of surgical training at Hôtel-Dieu envisaged a period of six years for *compagnons chirurgiens* to emerge as master surgeons.[2]

Development of elective surgery in the 1876–1886 period necessitated development of surgical training programs with young assistants living in hospital to care for the patients, assuming responsibility for their preoperative and postoperative supervision.

The Berlin-Vienna School of Surgery

The long line of descent and surgical eminence at the University of Berlin lasted from 1810 to 1882. Karl v. Graefe, a well known military surgeon, was the leader of the second, the Ziegelstrasse surgical clinic at the University, and Professor of Surgery over the years 1810–1840. His successors were Dieffenbach (1840–1847) and Bernhard Langenbeck (1848–1882), followed in turn by Ernst v. Bergmann (1882–1907). Langenbeck's most famous pupil, Theodor Billroth, provided strong leadership in surgery at the University of Vienna (1867–1894), followed by productive proteges that continued the great influence of the Berlin-Vienna School into the 1930's.[23]

The surgical clinic at the Charité began somewhat earlier than the Ziegelstrasse. Christian Mursina, Professor of Surgery (1787–1815), first brought distinction to this the first University of Berlin surgical clinic. Johann Rust was Mursina's successor, and had spent some time with Vincenz v. Kern in Vienna. Like v. Graefe of the second Ziegelstrasse clinic, Rust also was a military surgeon of prominence.[11] The last great leader in the Charité clinic was Ferdinand Sauerbruch (1875–1951), an innovative thoracic surgeon who added distinction to the School through his own work and the development of a brilliant school of surgeons.

Langenbeck's extraordinary success at the Ziegelstrasse Clinic was owing primarily to unfeigned enthusiasm for surgery and to an engaging and winsome personality; he was a talented and skillful operating surgeon, a brilliant lecturer who succeeded in communicating his enthusiasm for surgery to a host of proteges, but who made no significant durable contribution to surgery's advance. For 14 successive years, Langenbeck was president of the German Surgical Society, a circumstance that tells much of his commanding personality. His pupil, Theodor Billroth, probably the greatest teacher of surgery during any period of time, was never honored by the Presidency of the German Surgical Society, though he was made an honorary member during the terminal decade of his long and productive career. The eminence of the Langenbeck-Billroth School was continued through Billroth's brilliant pupils, Johann Mikulicz of Breslau and Anton v. Eiselsberg in Vienna; Mikulicz died in 1905 at age 55 of a gastric cancer, but did distinguished

work in surgery at the University of Breslau during a brief professoriate (1890–1905). The Billroth influence continued also through his attractive pupil, Anton v. Eiselsberg, professor of surgery at the first surgical clinic in Vienna from 1901–1938. When Hitler demolished the influence of the universities in Germany prior to the beginnings of World War II, the brilliant German school of surgery that had remained pre-eminent for more than 125 years came to an abrupt end.[23] It is beginning to show signs of survival.

American Schools of Surgery

Successively a number of surgical schools of quality developed in America beginning with the University of Pennsylvania in the terminal years of the eighteenth century. Over the years such distinguished surgeons as Philip Syng Physick, his nephew Dorsey, Samuel D. Gross, W. W. Keen, Isidor Ravdin, John P. Gibbon, Jr., and Jonathan Rhoads emerged.

The New York school gained prominence in the nineteenth century under the leadership of Valentine Mott, Wright Post, Willard Parker, Charles McBurney, the physiologist-surgeon Samuel Meltzer, Stephen Smith, and Allen Whipple, representing several New York schools and hospitals.

The Boston school of surgery acquired distinction in the mid-nineteenth century with the development of anesthesia under the aegis of the dental surgeons William T. G. Morton and Horace Wells and the great surgeon John Collins Warren at the Massachusetts General Hospital. Henry J. Bigelow, Harvey Cushing, Elliot Cutler, Edward Churchill, Robert Gross, Francis Moore, and Richard Egdahl successively brought added distinction to the Boston School of surgery, largely Harvard dominated. The fine leadership exhibited by the Boston school of surgeons continues after more than a century.

The Hopkins in Baltimore under the leadership of Daniel Coit Gilman and William H. Welch developed a great medical school following the German university pattern. When William S. Halsted emerged at The Hopkins as a great surgeon at the turn of the century, leadership in American surgery went to The Hopkins.[23] Halsted's long professoriate (1889–1922) was marked by scholarship of a high order, surgical innovations and development of a great school of versatile surgeons. With Halsted's death, leadership in surgery at The Hopkins enjoyed a pleasant and peaceful slumber under the direction of Dean Lewis, an effective undergraduate teacher who manifested no interest in research. When Alred Blalock, a Hopkins graduate, whose training in experimental surgery was at Vanderbilt in Nashville, returned to The Hopkins in 1941, the luster of the Halsted period was restored. Blalock, like his predecessor Halsted, developed a great school of surgeons through creative research, innovation, and superior teaching, a luster that lost some fragments of that distinction on Blalock's death in 1964.

At the turn of the century, a strong school of surgery emerged in Chicago under the leadership of the surgeon-pathologists, Christian Fenger, Nicholas Senn, and J. B. Murphy, an influence continued under a second generation of productive surgeons, represented by Arthur Bevan and Evarts Graham, whose brilliant professional career was spent at Washington University in St. Louis. The influence of a third generation of Chicago surgeons is represented in the work of Lester Dragstedt and Charles Huggins, and a fourth under the leadership of David Skinner and Lloyd Nyhus.

As in most countries of western culture there have been many distinguished American surgeons who have not developed schools of surgery, notable amongst them are J. Marion Sims, George W. Crile, Sr., William Mayo, and Rudolph Matas, all of whom lent a distinctive flavor to American surgery.

Important schools of surgery dot the entire geography of our great land today. None can claim preeminence in all the sectors of learning that have distinguished great schools of surgery in the past. Surgical luminaries such as John Hunter, Pierre Desault, Vincenz v. Kern, Bernhard Langenbeck, Theodor Billroth, William Halsted, Evarts Graham, Allen Whipple, and Alfred Blalock appear only periodically on the scene. Their emergence as great surgical leaders is deserving of careful study and continued scrutiny.

The Minnesota Plan of Surgical Training

George Edgar Vincent, a transplanted Daniel Coit Gilman, came to the University of Minnesota in 1911 as its third University President; during the short six years of his tenure from 1911–1917, he recreated a number of mediocre, sleeping, self-satisfied, unproductive colleges into a true university through the simple expedient of the power of appointment. He brought to the University a number of great leaders in many disciplines whose durable influence still can be felt within the halls and walls of the University. He, like Gilman, employed a university's finest possession, the power of appointment, to build a great faculty.

One of my predecessors, James E. Moore, was a keen advocate of aligning the department of surgery with the university's Graduate School, an arrangement he effected in 1914, providing surgical trainees with exposure to a basic medical discipline. This surgeon was granted the rare privilege of assuming the direction of the department in January 1930 only because two far more eligible surgeons who had come to be interviewed declared "there is nothing here and there never will be." They obviously had not stayed long enough to savor the growing spirit of inquiry which Vincent instilled into the institution. As our training program for surgical residents developed, it too came in post-World War II days to be of a length similar to that described by Halsted several decades earlier (1904). However, of that eight to ten year training period, half was spent in the experimental laboratories of surgery and in those of another basic discipline, usually physiology. In the experimental laboratory, trainees learned how to operate and to think, and how to create experimental models that could provide reliable answers to well directed queries. When I assumed direction of the Department, we had one surgical fellow (resident); when I informed him I was contemplating appointing another he threatened to quit saying there was not enough work for two fellows. I was able to persuade him that on our 130 surgical beds there certainly should be enough work for many more. During the last decade prior to my superannuation, July 1, 1967, we actually had 100 surgical fellows on the united surgical services of approximately 175 beds for surgery and its specialties comprising neurosurgery, orthopedics, and urology; there were 85 fellows in general surgery and 15 surgical fellows in the three named specialties. Approximately half of the surgical trainees in general surgery, as explained above, were in experimental laboratories of the department or in the laboratories of physiology, in which areas trainees, aiming for an academic career, spent approximately one-half of their overall training period. The training program for the community oriented surgeons was approximately five years in length with primary emphasis upon clinical exposure.

Only 15 per cent of the total budget for support of the surgical faculty and trainees came from Minnesota legislative support. Prior to World War II, a significant segment of our research support came from affluent patients from whom this surgeon had exacted no fees. If he was sent money, he gave it to the University in the name of the donor, who then promptly adopted a posture of making a very generous contribution annually, persuading some of his friends to join in the endeavor. This practice was encouraged by an annual research luncheon in which young surgical trainees presented brief resumes of their work, often accompanied by demonstrations. Without ever having asked affluent patients and their friends for a donation, $30,000 to $100,000 poured in annually during the Christmas Season for support of our training program. With the largesse of Uncle Sam and the generosity of the American people through its Congress after World War II, money became available in liberal amounts in support of research as well as for training programs. Ours was essentially an unconventional type of surgical training program. Several leaders in American surgery disapproved of it; yet when visiting committees came for a periodic inspection, though often we encountered difficulties, usually a voice or two in such committees favoring continuance of support sufficed to make it possible for the program to continue. There were a few periods, I must confess, in which it seemed our training period was threatened with loss of generous federal support, a circumstance affirming how closely representatives of the National Institutes of Health committees adhered to traditional and conventional lines. Said Maurice Maeterlinck (1909), Belgian Nobel laureate, "10,000 guards bind each of us to tradition, not easily set aside."

Of the approximately 800 surgical trainees enrolled in the graduate school during this surgeon's tenure as Chairman of the Department, we had more than 100 who achieved Master's degrees in surgery and a like number of Ph.D.'s. One of my colleagues, Dr. Arnold Leonard, pointed out in an interrogatory in May 1967 that "33 full-time professors and heads of departments and surgical specialties had evolved from this program; an additional 30 were occupied full-time in academic positions at a lower rank than full professor; more than 100 surgeons had continued in some form of academic surgery."[13, 19] A few more trainees still in the training program (1967) have since joined the academic arena.

The primary function of the chairman of a department, in this surgeon's view, is to create an atmosphere friendly to learning. If the chairman succeeds in communicating his enthusiasm for research, scholarship, and teaching, his objective will be communicated directly to his proteges.

Our training program was directed obviously primarily at training surgeons for the academic arena. Of the 800 trainees engaged in the program over the 37½ years of the author's tenure, approximately 12.5 per cent remained in the surgical academic arena in some capacity. This was obviously a large number of surgical trainees for a single surgical clinic. Approximately half that number, however, were constantly engaged full-time in our research laboratories. There they became skillful, talented surgeons where abundant opportunities for operating on animals were available daily to them in the course of their experiments. In fact, our finest surgeons enjoyed this exposure and approach to surgery. The care, management, and preparation of patients for operation was learned on the wards. The technique of performance of operations they had already mastered in the experimental laboratories.

We did not employ the pyramidal scheme of choice of fellows or residents in which at the conclusion of each school year, only the best man in groups at various levels of training was chosen to continue in the program, the others being dismissed—a scheme still continued in some universities. At Minnesota we came by several good scholars in this manner who had been dismissed from other programs. My view always has been that good men are scarcer than money. If we had two or three good men available between whom it was difficult to choose, but only money for one, I believed it wise to take all three. Sympathetic affluent patients and friends quickly came to our rescue, eager to support promising individuals for a few years in reaching their goals.

On a study trip abroad from 1927–1928, and again in 1959, I observed frequently that the director of a German surgical clinic made most of the important decisions. In my view, this is entirely wrong. When strong men are given a staff appointment, they should, I believe, always have the opportunity to make their own judgments. In long years in University circles, I have had the opportunity to observe occasionally a talented administrator making strong appointments, yet intervening and interfering to modify or change the decisions of his own appointees, a reckless practice that undermines the morale and effectiveness of strong appointments. Appointees must be allowed to make their own mistakes and to learn how to correct them. Maturity is arrived at far more quickly and readily by this manner of direction in my view. If an appointee asked for advice and suggestions, I would indicate what my decision and choice of procedure would be, while insisting that the new staff member must decide for himself what is best and wisest for him to do.

Shared opportunity is, I believe, the finest paymaster of the surgical academician. As the number of our surgical trainees grew, our policy was for each member of the staff to move over a bit, permitting the surgical fledglings to share with their seniors the opportunity enjoyed by their elders. Sharing is a winsome word, one of the finest in our vocabulary. A primary philosophy of the department rested on the thesis that the rewards of shared opportunity were great for all, and collectively for the department.

How Is Tomorrow's Creative Surgical Academician to Be Recognized?

It is one of the functions of medical educators to recognize young talent before the whole world concedes it. Obviously, there is some risk involved but the potential gain to a faculty in selecting young leaders with great potential is undoubtedly one

of the hallmarks of how strong faculties are developed in our institutions of learning. Current Search Committees on the prowl for young surgical talent almost invariably ask "But can he operate?" Cultivation of Paderewskis of the scalpel without question creates superb technically skilled surgeons. Many university surgical clinics and the American Board of Surgery too are placing great emphasis upon *performing* operations to the neglect of the importance of *observation*. Surgeons of the Kocher-Mayo era of the early decades of this century stressed observation. They visited innovative clinics from which new procedures were emerging, a practice not so frequently observed today.

Training surgeons for the academic arena necessitates that a portion of their training be spent in another basic discipline. Halsted's trainees spent eight years beyond the internship or a total of nine years as house-officers. Halsted was able to create a host of versatile, talented surgeons, but only a few creative and innovative surgeons emerged from that group, notably Harvey Cushing, Walter Dandy, and Emily Holman. Every patient in need of surgery would like to find the most talented and skilled surgeon available for his operation. However, it is to research far more than to technology to which we must look for surgery's advance.

Recent correspondence with a number of current day leading surgeons in western Europe suffices to indicate that the primary address of Search Committees in the selection process of a departmental chairman too is, Can He Operate? In his early years Halsted said a surgeon must operate every day to become a proficient operating surgeon.[9] Willis Gatch (1952), a Halsted trainee of 1910 quoted Halsted as having said "Surgery would be great fun if one did not have to operate," obviously reflecting a radically different point of view, occasioned in part undoubtedly by a serious retrospective view of his own accomplishments.[6] Every surgical faculty should have one or two Paderewskis of the scalpel on its staff. The most important distinction of a true university is to create and to think; to strive to say the first rather than the last word. Dissemination of knowledge very obviously is very important for the public good; however, in this surgeon's view, such is the responsibility of colleges rather than of universities.

The Power of Appointment

Under the leadership of Dean William H. Welch with the advice of John Shaw Billings, Gilman developed at The Hopkins in Baltimore the most impressive medical faculty in America. Mall in anatomy, Abel in pharmacology, Osler in medicine, and Halsted in surgery were among the primary appointees that established The Hopkins as the finest medical faculty for that era in America. Since World War II and the largesse of Uncle Sam in supporting medical research, The Hopkins' full-time program, geographical for clinical appointments, has been almost universally adopted in our country, a scheme that augurs well for teaching and research.

Rise and Fall of Surgical Schools

A few schools of surgery have remained dominant for more than a century. Salerno in the thirteenth century gave way to the illustrious Bologna school which produced surgeons of such competence that many of their names are still known to us: Theodoric, Bruno, Saliceto, Lanfranchi, and Henri de Mondeville. Bologna was succeeded in turn by Montpellier and by famous schools of surgery in Paris, Edinburgh, Vienna, Berlin, and Baltimore. The duration of dominance of surgical schools appears to be more closely related to qualities of leadership than to other factors.[23] In the final analysis, a school is measured by the contributions of its faculty to medical advance, and by the quality and ability of its proteges to carry on the school's tradition. Pathfinders and trailblazers are always remembered. The genesis of the rise and decline of schools is not susceptible of ready assessment. Vital factors are the directional course of the institutional and national aims, the status of the economy, the pride of communities in their institutions of higher learning, the level of national community interest in and support of research. Even more significant, however, is the internal environmental climate of the school. A lively, enthusiastic, and fervent zeal is like a highly contagious disease. It was the primary source of Langenbeck's great influence upon German surgery. Billroth's school of surgery produced several leaders who carried on the Langenbeck-Billroth

tradition, notably Mikulicz and Eiselsberg. The ardor of motivation, sincerity of selfless dedication, accompanied by an obvious respect for scholarship and love of learning, these are amongst the finest architects of a creative and innovative environment so essential for the development and endurance of a school.

Summary

A variety of talents characterize the leaders of various eminent schools of surgery over the past two centuries that eludes precise delineation. There appears to be no standard pattern or model of performance. This brief narrative depicts some of the striking and primary qualities that have distinguished the leaders of a few notable schools of surgery during this period.

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Radiographic Media in Urology

The Discovery of Excretion Urography: Historical and Developmental Aspects of the Organically Bound Urographic Media and Their Role in the Varied Diagnostic Angiographic Areas

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Uroradiology and its clinical applications are intimately associated with the development and investigation of various radiographic media. For historical purposes, one may consider two separate phases.

PHASE I: INORGANIC MEDIA ADMINISTERED VIA THE CYSTOSCOPE

Phase I substances under discussion are (1) colloids: collargol and argyrol; (2) crystalloids: the inorganic iodides and bromides; and (3) gases: oxygen, carbon dioxide, and air.

To point out the tremendous contribution that the successful nontoxic organically bound iodide compounds have made to medicine and surgery as a whole, I will describe the early attempts at delineating the urinary tract on x-ray film which were followed at times by dire consequences.

Visualization of Urinary Tract

The first pioneer attempt at visualizing the urinary tract was made by Tuffier in 1897, suggesting the combination of an opaque ureteral "styletted" catheter and radiography. In 1901 Schmidt and Kolischer used "styletted" catheters to delineate the course of the ureter and pelvis. In 1904 Klose reported on the use of "styletted" catheters in a case of double ureter; he also suggested the injection of an emulsion of bismuth into the pelvis and ureter through a catheter. In the same year, Wulff outlined the urinary bladder with a suspension of bismuth subnitrate.

In 1905, Voelcker and von Lichtenberg used a 2 per cent collargol for cystography, and in the following year they published their results on retrograde pyelography by means of this substance injected through a ureteral catheter, and were thus the first to outline in a satisfactory manner the pelvis and calyces in the human subject on x-ray film. Subsequently other observers utilized stronger solutions of collargol as well as argyrol and a 5 per cent emulsion of silver iodide, all silver compounds. Although in some hands the colloidal silver media had met with success, their use was abandoned since fatalities had been encountered. Braasch and Mann, injecting the pelvis of dogs, found that silver preparations act as foreign bodies, frequently causing multiple foci of necrosis. Eisendrath, based on injecting known amounts of collargol under known pressure into the kidneys of dogs, believed that the majority of ill effects were due to the fact that when the capacity of

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the pelvis was exceeded by the injected fluid, the solution was either forced into the loose tissues around the renal pelvis or into the renal parenchyma, and from there into the general circulation with deposits in the various viscera. At pressure below 30 mm Hg he found that practically no collargol entered the kidney parenchyma or infiltrated the peripelvic tissues of the dog. However, at higher pressures and when the capacity of the renal pelvis was exceeded, large infarcts or small deposits of silver in the kidney or perirenal tissues, hemorrhages into the spleen or liver, and various lung changes, such as emboli, hemorrhagic infarcts, pneumonia or acute pulmonary edema, might occur. Collargol had been found to cause death from urinary suppression and hemorrhages from the bowel, mouth, and nose in the human patients. It is obvious then that the choice of a medium for retrograde pyelography became a very serious consideration, since any overdistention of the renal pelvis may produce an invasion of the local and general circulation.

Improvement on the colloidal silver media came with the introduction by Burns in 1915 of the first crystalloid, a 10 to 15 per cent solution of thorium nitrate dissolved in sodium citrate and made neutral with sodium hydroxide. Irritative phenomena, occasional fatalities, toxicity of the solution on standing, and the ease with which moulds grew on it were some of the objections raised. Nevertheless, for want of a better medium, it was one of choice for three years.

A notable advance occurred in 1918 when Cameron suggested sodium and potassium iodide, and Weld proposed sodium and potassium bromide. The potassium salts in both cases were excluded because of the depressant effect of the potassium ion, particularly on the heart.

With regard to the comparative value of sodium iodide and sodium bromide for pyelography, Cameron, in a carefully detailed work, proposed the former on the following grounds. (1) Its greater molecular weight gives a radiographic shadow of great density with a solution at much lower concentration. (2) Iodine is a member of a group of elements which possesses the property of selective absorption of the x-ray, particularly those of high penetration. Cameron found that one iodine atom has the opacity of three bromine atoms to the hard rays. (3) A 13.5 per cent iodide solution is as opaque as a 25.2 per cent sodium bromide solution, and more opaque than the standard thorium solution. (4) The osmotic pressure of sodium iodide in the concentration used for pyelographic purposes is only slightly greater than that of concentrated urine and, of all the various substances used, is the least hypertonic.

Hypertonicity

The question of hypertonicity becomes important when the work of Graves and Davidoff is taken into account. They observed, with the injection into the bladder of rabbits of 40 cc of 25 per cent sodium bromide at 17.4 mm Hg of pressure, that there was an increased irritability of the vesical musculature which gave way to distinct depression. As the filling of the bladder progressed, its posterior wall developed a pale, silvery sheen; the musculature became blanched as if anemic. With greater distention extreme edema developed which involved the posterior dependent portion of the bladder and extended into the adjacent tissues. Thrombosis of small vessels occurred at times. When emptying was permitted, they found the bladder completely crippled. The anterior wall, however, protected by the air bubble and away from the solution, contracted normally. They could reproduce these findings using 36.4 per cent sodium iodide and 25 per cent sodium chloride solutions. On the other hand, physiologic bromide solution, isotonic with blood, had no more effect than isotonic sodium chloride. They also reported that 14.5 per cent sodium solution was innocuous from the standpoint of the effect of hypertonicity and yet yielded good x-ray plates. Mention should be made of the other media and procedures advocated in the past and which, in many instances, were subsequently discarded.

Objections to the use of oxygen, air, or carbon dioxide are their confusion with overlying intestinal gas, difficulty in maintaining full distention of the pelvis and ureter, and air embolism. Umbrenal or lithium iodide is expensive and frequently irritating, producing spasm of the calyces and pelvis, making interpretation of a pyelogram difficult at times. Lipiodol is of an oily consistency, has a tendency toward globule formation in the presence of water, is unsuitable for pyelography, and is expensive. Umbrathor, a colloidal suspension of thorium dioxide, is viscid,

like lipiodol, making emptying by the renal pelvis difficult, and in cases with mild upper urinary tract obstruction, becomes a source of irritation. Its use in cystography, however, has definite advantages. In one case in particular, that of a flat submucosal type of bladder carcinoma in which sodium iodide as a cystographic medium did not depict the filling defect, umbrathor very concretely demarcated the circumference of the growth. The question of emptying of the medium in the case of the bladder is of no consequence. Objections to Neo Silvol in 20 per cent concentration are similar to those for lipiodol and umbrathor.

PHASE TWO

I am deeply appreciative of the honor that you have bestowed on me in presenting me with the Valentine Award. Ferdinand C. Valentine, one of our early pioneer urologists, in whose honor this cherished award has been established, died in the early part of this century. I venture to say that he, with his interest in the furtherance of knowledge, would have been amazed at and delighted with the developments in the field of urology during the past 30 years, particularly in the area of excretion urography with the introduction of the organically bound iodide urographic compounds, which have opened up many new diagnostic and therapeutic avenues in medicine. During Dr. Valentine's lifetime it was possible to obtain very little diagnostic data that enabled one to correct various disorders with a degree of accuracy, especially in the area of pediatric urology. The objectives of the Valentine Award afford opportunities for investigators to continue to contribute to the further scientific progress of urology.

Urography and its clinical application is intimately associated with the development and the investigation of various radiopaque media. For historical purposes, one may consider two separate periods in the development of these media, namely, that of the inorganic iodide radiopaques, administered cystoscopically, and the more recent one, that of the organically bound iodide compounds, administered intravenously, the latter being responsible for the development of excretion urography and other diagnostic fields in medicine.

On this occasion I shall confine myself to the present era, namely, to the development of the organically bound iodide compounds and their present role in urography.

The organically bound iodides as urographic media were responsible for the successful development of excretion urography. An historical background is therefore not amiss.

In 1923, Rowntree and his co-workers,[19] administering a 10 per cent solution of sodium iodide intravenously and also by mouth, reported the visualization of the urinary bladder and, in some cases, though faintly, the renal pelvis and ureter. Hryntschak,[9] in 1928, employed a series of bromine and iodine compounds identified only by numbers, some of which were aromatic in nature. Roseno,[22] in 1928, used a double compound—sodium iodide-urea. These compounds, as well as all others attempted, fell into disuse because of reactions in some cases; in others, because of the extremely large dose required and the poor results. All the investigators who had utilized the halogen compounds found that these could not be given in sufficient quantities to be of any practical value for excretion urography, though under favorable conditions in occasional cases, the kidney, pelvis, calyces, and ureters could be made out.[13, 23, 41, 49, 50] A. Roseno stressed the importance of the functional aspects of the problem. In a discussion of Roseno's paper and remarks by Hryntschak at the Eighth Congress of the German Urological Society in September 1928, reviewing the accomplishments up to that date, von Lichtenberg stated that his experience in this area had been disappointing and that more progress was not likely.[42]

In 1929, I presented papers on my researches and successful development of Uroselectan (in our country called Iopax) for intravenous urography. It may be of interest to recount the thoughts, the steps, and the details that led to the final satisfactory result.

In 1928, under a Libman Fellowship, I went to work at the Altona Krankenhaus in Hamburg, Germany, where Professor Lichtwitz was using a compound called

Selectan-Neutral for the treatment of coccus infections in man. This compound, iodopyridon-methyl, one of a group synthesized by the chemist Professor A. Binz, had previously been used for coccal infections in cows. Since this compound contained iodine (54 per cent), an element known for its roentgenographic properties, it occurred to me that it might be of value in visualizing the urinary tract. I conducted simultaneous chemical excretion determinations, toxicity, and roentgenologic studies. These studies revealed that the compound was promptly excreted in the urine, and that roentgenologic examinations in the rabbit and human revealed encouraging results in that the kidney parenchyma and urinary bladder could be visualized not infrequently after the intravenous administration of the drug; the renal pelvis and ureter, on the other hand, were for the most part poorly seen. In one case, that of a high occluding ureteral calculus, satisfactory visualization of the upper urinary tract was also demonstrated. Experiments in rabbits revealed that 0.2 gm per kg of body weight was tolerated without demonstrable disturbances. This would be equivalent to approximately 12 gm of substance (6.48 gm of iodine) as the upper limit for an animal weighing 60 kg. In humans considerably less than this amount was used. Marked individual differences in tolerance were noted. Disturbing factors associated with Selectan-Neutral were diplopia, vomiting, nausea, and headache. Oral administration produced similar results. In no case, however, were the symptoms of such a nature as to deter me from continuing with this work. Simultaneous excretion studies limited to quantitative determination of the iodine component revealed that 75 to 80 per cent of the injected iodine was recovered in the urine. The attained results, although not sufficient for practical purposes, pointed to the potential of the methodology and warranted continued investigation. The problem then resolved itself in modifying Selectan-Neutral in order to accomplish the following results:

1. To diminish the toxicity through the substitution of the methyl radical in order to decrease toxicity and thus permit the administration of a larger dose, thereby attaining a higher concentration of the excreted iodine component, a determinant factor for radiologic success. (The observation of double vision led me to the suspicion, at least empirically, that the methyl radical of Selectan-Neutral might be responsible for the toxic manifestations.) The latter thought was the stimulus for continued investigation that led to the ultimate successful outcome.
2. To increase the solubility by means of a substituted radical so that a larger dose could be administered.
3. To increase the iodine content of the molecule.

After carrying out these investigations for about seven months in Hamburg-Altona, I presented the ideas and results with Selectan-Neutral to Professor Binz in Berlin and sought his aid. He subsequently furnished me with two separate di-iodo-pyridon compounds with the methyl radical substituted (Fig. 1). On returning to Hamburg, both of these compounds, because of their poor solubility, were administered by mouth, not intravenously, to dogs. Neither one was absorbed and both produced x-ray shadows of the intestinal tract.

My investigations were then transferred to the large urological service of Professor von Lichtenberg at the St. Hedwig's Krankenhause in Berlin. This also afforded me close contact with Professor Binz, who followed these investigations with great interest and was confident that the specifications could readily be fulfilled. Meanwhile, I continued to work with Selectan-Neutral at the St. Hedwig's

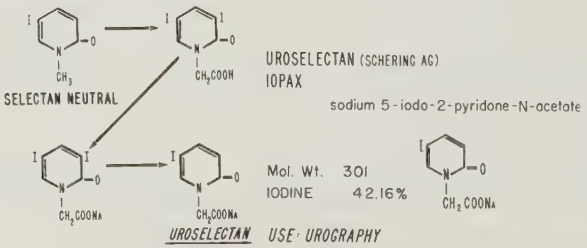

Figure 1. The structure of Selectan and Uroselectan.

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Figure 2. Title page of the initial article on the use of Uroselectan in urography. (*From* Swick, M.: Darstellung der Niere und Harnwege im Roentgenbild durch intravenoese Einbringung eines neuen Kontraststoffes, des Uroselectans. Klinische Wochenschrift, 8:2087–2089, 1929.)

DARSTELLUNG DER NIERE UND HARNWEGE IM RÖNTGENBILD DURCH INTRAVENÖSE EINBRINGUNG EINES NEUEN KONTRASTSTOFFES, DES UROSELECTANS

Von

Dr. M. SWICK, New York.

Aus der Medizinischen Abteilung des Altonaer Krankenhauses (Prof. Dr. LICHTWITZ) und

d. Urol. Abt. des St. Hedwig-Krankenh. in Berlin (Prof. Dr. v. LICHTENBERG).

Das von Prof. BINZ und Dr. RÄTH dargestellte Selectan-Neutral ist in der Medizinischen Abteilung des Altonaer Krankenhauses seit längerer Zeit bei Kokkeninfektionen der verschiedensten Art versucht worden. Therapeutische Erfolge bei Infektionen der Gallenblase und der ableitenden Harnwege legten es nahe, die Ausscheidung zu untersuchen. Es wurde festgestellt, daß diese sowohl durch die Niere als auch in die Galle erfolgt (Dr. ERBACH).

Figure 3. Bilateral renal calculi in a 54 year old man with left side pyelectasia and outlet resistance (partial obstruction) secondary to angulation and fixation of the ureter at the ureteropelvic junction. Atonic dilatation of the renal pelvis and ureter on the right side. (*From* Swick, M.: Darstellung der Niere und Harnwege im Roentgenbild durch intravenoese Einbringung eines neuen Kontraststoffes, des Uroselectans. Klinische Wochenschrift, 8:2087–2089, 1929.)

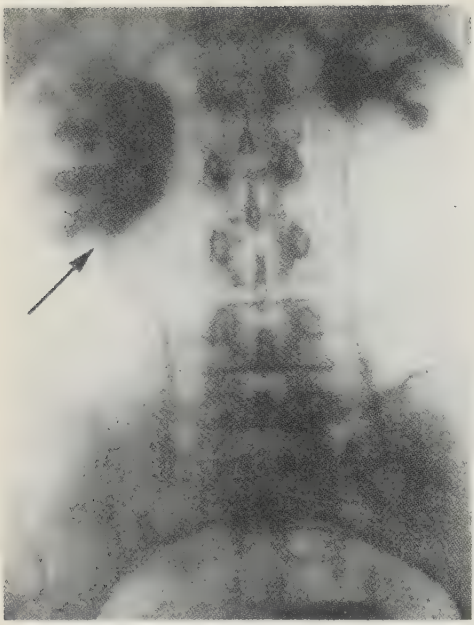


Figure 4. Reproduction for the second article on the use of Uroselectan (Iopax) in Urography 11B. The original legend reads: A 36 year old female patient with right side obstructive kidney visualized at the moment of emptying. Left side completely visualized normal urinary tract is observed. (*From* Swick, M.: Darstellung der Niere und Harnwege im Roentgenbild durch intravenoese Einbringung eines neuen Kontraststoffes, des Uroselectans. Klinische Wochenschrift, *8*:2087–2089, 1929.)

Krankenhaus awaiting the development of modified compounds with the pyridon nucleus. In order to obtain greater solubility and eliminate toxicity, Professor Binz and Dr. Rath of the Agricultural College of Berlin (the Chemical Institute) prepared the modification of the Selectan-Neutral in which the methyl radical was replaced by a sodium acetate radical. Solubility was also increased by lowering the iodine content from the di-iodo-pyridon to the original mono-iodo-pyridon nucleus of Selectan-Neutral. This new preparation, named Uroselectan, fulfilled the necessary requirements (Fig. 1). In 1930 Professor Lichtwitz, at whose clinic my work was initiated, recorded the sequential development of the successful compound,[15]

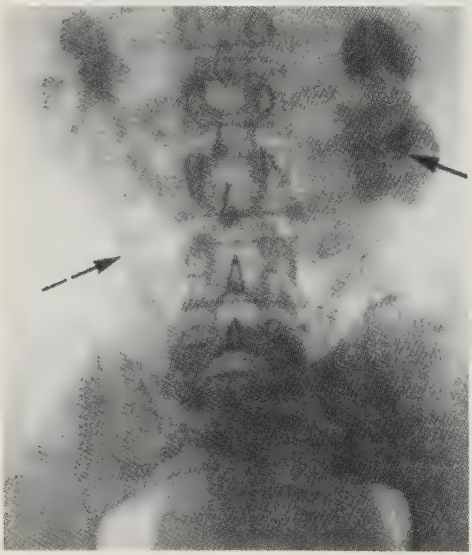


Figure 5. From the second article on the use of Uroselectan (Iopax) in Urography 11B. The original legend reads: Horseshoe kidney in a 36 year old male with calculi and considerable dilatation of both renal pelves, particularly the left side. The congenital abnormal course of both ureters, issuing from the lateral aspect of the pelves is clearly visualized.

stating "Herr Dr. M. Swick aus New York hat diese Prüfung durchgeführt. Ihm verdanken wir die Uroselectan-methode." (To Dr. Swick of New York we owe the Uroselectan method.)

Uroselectan is nontoxic with the dose used, highly soluble in water, neutral in reaction and, under normal conditions, excreted unchanged through the kidney in sufficiently high concentration to yield good x-ray visualization. Figures 2 to 5 represent my first roentgenologic successes published in the Klinische Wochenschrift in November 1929, and in the Zeitschrift für Urologische Chirurgie, recording my lecture and presentation before the Ninth Congress of the German Urological Society, held in Munich in September 1929.[16, 24–28, 43, 45]

Uroselectan is well tolerated intravenously. Rabbits could tolerate repeated daily doses of 3 gm per kg of body weight. Using this latter figure as a basis for calculation, a 60-kg human, theoretically, could receive about 180 gm of the substance. The iodine content of Uroselectan is 42 per cent, corresponding to 75.6 gm of iodine of the above-calculated 180 gm. The preparation is more than 50 per cent soluble in water. The large amount of iodine is held in solution in tightly-bound organic form, which is excreted in the urine unchanged. With normal kidney function, 85 to 95 per cent of Uroselectan is excreted in the urine and can be recovered as such. Thus one can conclude that the drug undergoes no degradation in the body and probably no transformation. Quantitative determinations of the excreted substance can form the basis for a gross test of renal function. About three fifths of the substance is excreted during the first two hours, about one fourth during the next, and the remainder during the subsequent several hours (Fig. 6).

Permit me to digress for a moment from the main theme of this paper, in order to interpret a few pertinent observations bearing on renal function as it relates to excretion urography, as they presented themselves during the initial phases of the development and experiences with the excretory urographic media. Facts that may appear obvious today were stepping stones in the development of the concept and in the interpretation of some aspects of excretion urography as it related to renal function. For example, in the early days, nonvisualization in some instances was erroneously interpreted as being due to a nonfunctioning kidney with resultant unnecessary nephrectomy. Since excretion urography depends for its success on the functional activity of the kidney parenchyma, one should be cognizant of the

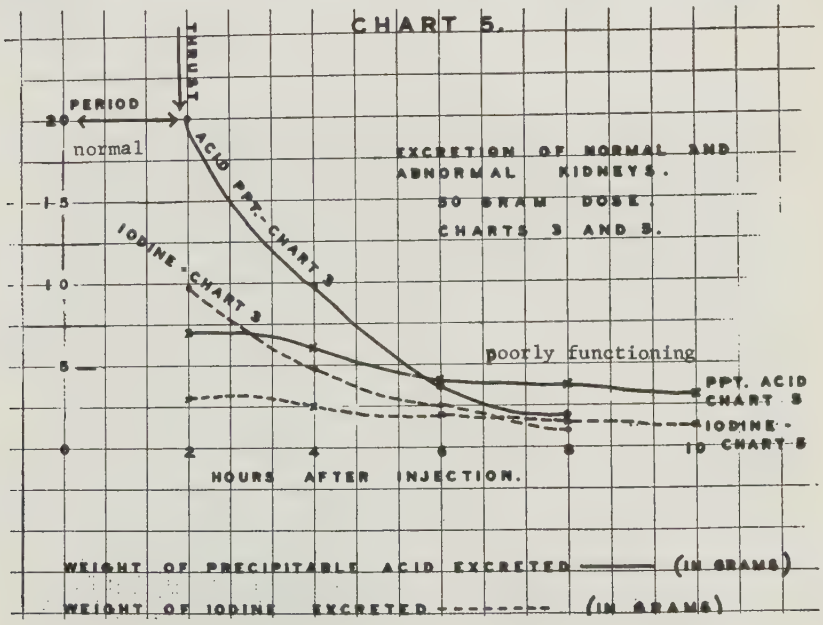


Figure 6. Curve of excretion of Uroselectan.

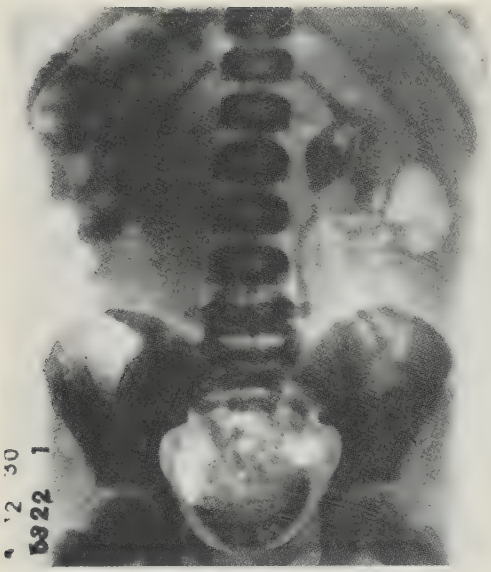


Figure 7. Intravenous urogram of a boy, aged 13, admitted for pyuria and left-loin pain, showing normally appearing and functioning right urinary tract and early filling of several sacculations (dilated calices) of the left kidney. Done with Uroselectan. (*From* Swick, M.: J.A.M.A., *101*: 1853–1855, 1933, with permission.)

renal and extrarenal factors that determine the net result in that functional activity; only in this manner can one properly interpret and evaluate the anatomic results obtained. The normally functioning kidney is able to excrete urographic substances in high concentration in a short period, which may be characterized as the "thrust-excretion ability of the normally functioning kidney"; roughly, 66 to 70 per cent of the opaque medium is excreted within the first two hours (See Fig. 6). It is upon this concentrating power of the kidney that the success of excretion urography depends. As a corollary, when this concentrating power is either impaired or absent, as in the poorly functioning kidney, the roentgenologic visualization is correspondingly poor or entirely absent.

Broadly speaking then, the degree of visualization depends on renal and extrarenal factors that determine renal excretion. However, in the presence of urinary tract obstruction, satisfactory visualization may still take place, although the normal rate of excretion required for roentgenologic purposes is impaired, provided that excretion still exists. Thus in cases of hydronephrosis, in which a reservoir mechanism is in effect, good visualization may still be obtained in late roentgenograms despite the existence of relatively little intact functioning renal tissue. An important concept to be derived from case illustrations bearing upon this consideration is the following: that in cases of hydronephrosis the intensity of roentgenologic shadow is not always a quantitative criterion for the amount of intact healthy renal tissue present, nor one for determining the type of therapeutic procedure. The following is an example of this principle:

Figures 7, 8, and 9 demonstrate the intense visualization obtained in a case of a markedly advanced congenital hydronephrosis incidental to an S-shaped trapped ureteropelvic junction, even though only comparatively little intact renal tissue was found at operation.

Again, the functional activity of the kidney may be temporarily inhibited as a result of either occluding ureteral lesions or trauma, although the kidney parenchyma itself is intact. Under such circumstances opacification of the renal outline is not infrequently observed as a concomitant finding with nonvisualization of the renal pelvis and ureter. The concept of temporary functional inhibition may be valid in cases with nonvisualization of the urinary tract at one examination, which has been followed by the restoration of renal function with visualization of the urinary tract after the removal of the causative factor. Such experiences have been observed in cases following trauma, and in others from occluding lesions.

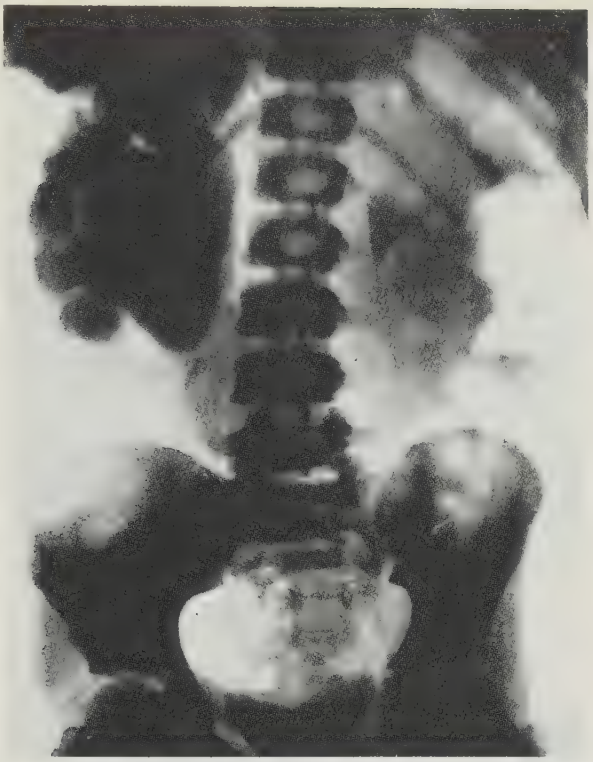


Figure 8. Urogram of same patient as in Figure 7 demonstrates the intense and complete visualization of the left hydronephrotic kidney, obtained several hours after injection, for practical purposes merely a large hydronephrotic sac. Done with Uroselectan. (*From* Swick, M.: J.A.M.A., *101*:1853–1855, 1933, with permission.)

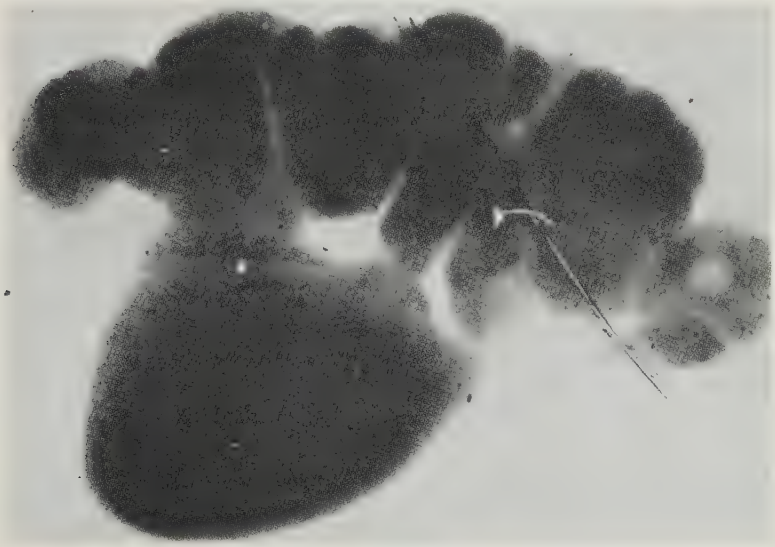


Figure 9. The injected nephrectomized specimen depicting the huge hydronephrotic sac.

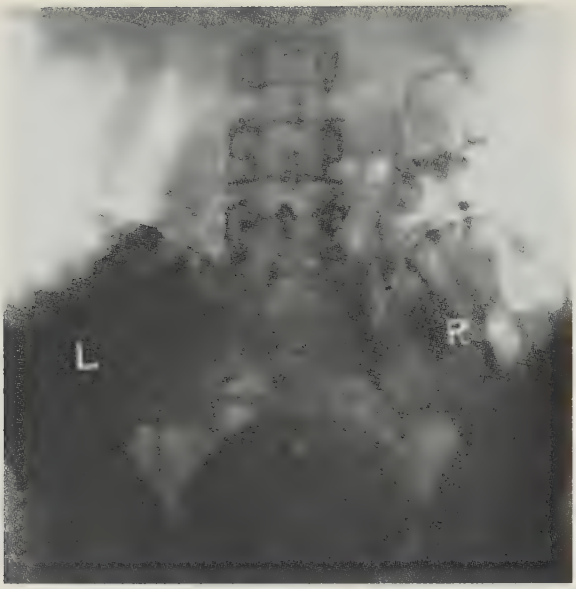


Figure 10. Absence of visualization of the left renal pelvis and ureter with opacification of the previously traumatized side; the double pelvis and forked ureter of the functioning right side is demonstrated.

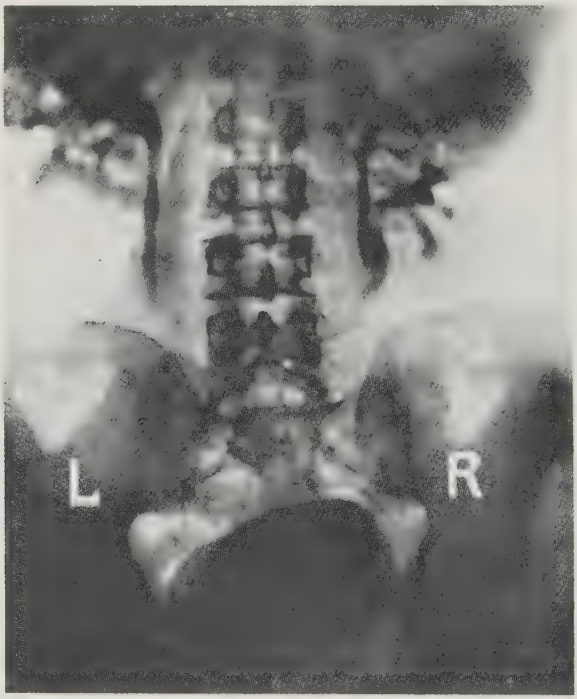


Figure 11. Subsequent intravenous urographic examination performed three months later now shows the return of function of the left kidney, demonstrating a normal left upper urinary tract plus the previous findings on the right side.

EXAMPLE. A 41 year old male patient was cystoscoped, and a left retrograde pyelogram was made. At that examination normal indigo carmine excretion from both ureteral orifices was seen. The pyelogram was normal. Following the instrumentation, hematuria and marked pain in the left loin set in and persisted for about a week. When both symptoms had subsided, intravenous urography was done. Absence of visualization of the pelvis and ureter with good kidney outline on the previously pyelogrammed and apparently traumatized left side, in addition to a double pelvis and forked ureter of the right functioning kidney, was noted (Fig. 10). However, another intravenous urographic examination made about three months later revealed now a normally functioning and appearing left urinary tract plus the previous findings on the right—a case of temporary functional inhibition following retrograde pyelography (Fig. 11). Therefore one should not always conclude that the kidney parenchyma is permanently damaged and beyond repair because of the nonvisualization of the urinary tract at a single examination. As a corollary, very late x-ray films after the intravenous administration of the urographic medium may yield invaluable information following the delayed visualization of the urinary tract in depicting the level of the occluding lesion and the status of thr urinary tract (Figs. 12 and 13). This case represents the first case I am aware of that demonstrates the contribution of excretion urography in depicting a congenital anomaly in a child, pointing up its potential and role in the further development of pediatric urology.

Returning to the original theme of the paper, the development of two subsequent compounds in Germany was of interest: these, which soon followed upon Uroselectan shortly after my return to the United States, were Neoiopax and Diodrast, which, you will note, have a pyridon nucleus similar to that of original successful Uroselectan (Fig. 14).[1, 44] Thus Uroselectan was the forerunner of the above two subsequent related compounds.

In 1931, further investigations of mine led to the formulation of another compound—Hippuran—which I presented and published in 1933. It was based on a metabolic principle differing from the above pyridon substances in that the iodine is organically bound to the 6-carbon-benzoic acid ring instead of the 5-carbon-nitrogen-pyridon ring of Uroselectan. Hippuran, a mono-iodo-benzoic acid derivative, interestingly and importantly bears similarity to our present urographic media, namely, Urokon,[46, 48] Hypaque,[8, 10–12, 17] Miokon,[6, 10, 47] Renografin,[11] and ConRay,[7] in that the latter are tri-iodo-benzoic acid compounds, Hippuran being, as mentioned, a mono-iodo-benzoic acid derivative. A detailed and illuminating treatment of the subject of x-ray contrast media is presented by Dr. James O. Hoppe

Figure 12. Marked dilatation of the left ureter, kidney pelvis, and calices in a boy 10 years of age admitted for hematuria. Right urinary tract is normal appearing, despite application of compression in midline. (Case of Drs. Leopold and Steward of the Lenox Hill Hospital, New York, New York.) (Reproduced by permission of J.A.M.A.[40])

Figure 13. Same patient as in Figure 12 with bladder partially empty, now demonstrating stricture (congenital) at the ureterovesical junction with marked dilatation of lower part of ureter, which was hidden on previous film by distended bladder. (Reproduced by permission of J.A.M.A.[40])

of the Pharmacology Section, Sterling Winthrop Research Institute, Rensselaer, N. Y. (Figs. 15 to 19) in his publication in Medicinal Chemistry in which he states the following:[7,8] "Sodium diatrizoate and the mixture of the sodium and N-methylglucamine salts of diatrizoic acid permitting aqueous solutions up to as much as 90%, therefore, appear to fulfill the requirements of the Swick hypothesis."

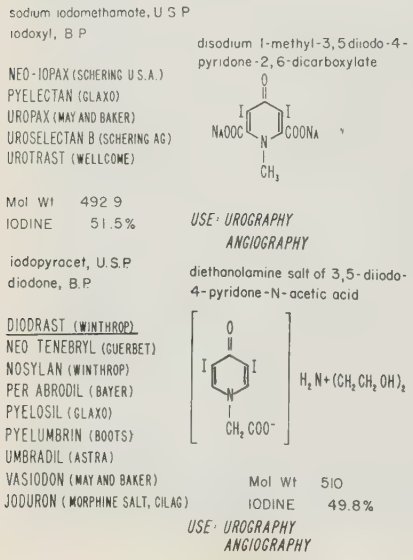


Figure 14. Chemical formulae of Neoiopax and Diodrast.

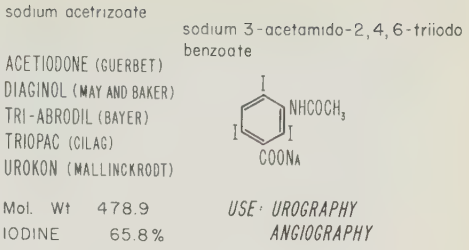


Figure 15. Chemical formula of sodium acetrizoate.

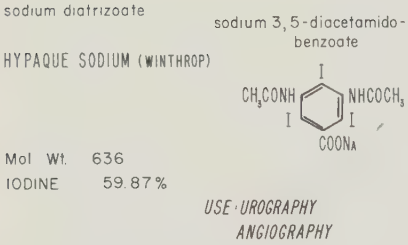


Figure 16. Chemical formula for sodium diatrizoate.

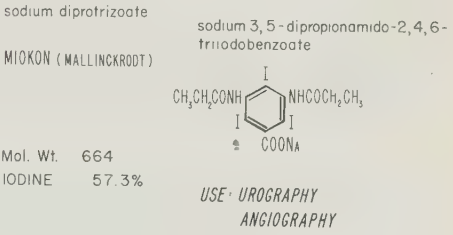


Figure 17. Chemical formula for sodium diprotrizoate.

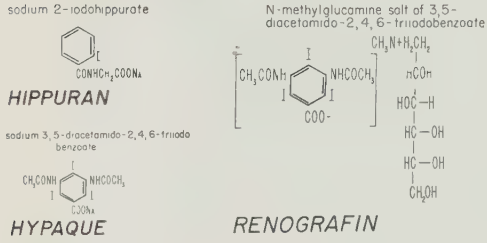
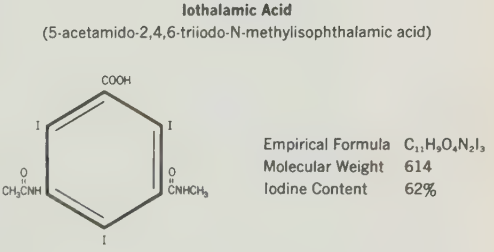
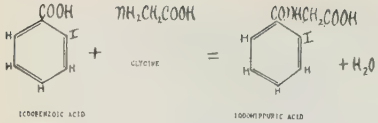


Figure 18. Chemical formulae for Hippuran, Hypaque, and Renografin.

Figure 19. Conray and Angio-Conray are sterile, aqueous solutions of the N-methylglucamine and sodium salts (respectively) of iothalamic acid. Conray, the 60 per cent solution of the N-methylglucamine salt, contains 282 mg of iodine per ml. Its viscosity is 4.0 cps at 37.5°C. Angio-Conray, the 80 per cent solution of the sodium salt, contains 480 mg of iodine per ml. Its viscosity is 8.4 cps at 37.5°C. Angio-Conray compares most favorably with sodium and methylglucamine diatrizoates 90 per cent, which contains 460 mg of iodine per ml and has a viscosity of 21 cps at 37.5°C.



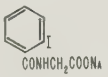


iodohippurate sodium

HIPPURAN (MALLINCKRODT)
HIPPODIN (LEO)

Mol. Wt. 363.1
IODINE 34.95%

sodium 2-iodohippurate



USE: UROGRAPHY

Figure 20. Chemical formula of iodobenzoic acid and Hippuran.

Hippuran (38.8 per cent iodine) administered in 50 per cent solution is an iodine derivative of a metabolic product, hippuric acid, normally found in the urine of the horse and man. It is the sodium salt of ortho-iodo-hippurate. It has long been known that the administration of benzoic acid or iodo-benzoic acid, after the detoxification with the amino acid glycine results in the excretion of the sodium salt of hippuric acid or iodo-hippuric acid (Hippuran) respectively (Fig. 20).[2, 5, 14, 15, 18, 20, 21, 29–39] Hippuran satisfies the necessary requirements for excretion urography both by the intravenous and oral routes (Figs. 21 and 22). Tagged ^{131}Iodine Hippuran has also been found of value as a test of renal function and a screening diagnostic method by means of the renogram.

In closing, I wish to point out that further important developments from the introduction of the tri-iodo-benzoic acid compounds—Hypaque, Renografin, Con-

Figure 21. Intravenous urogram shows normal-appearing urinary tracts.

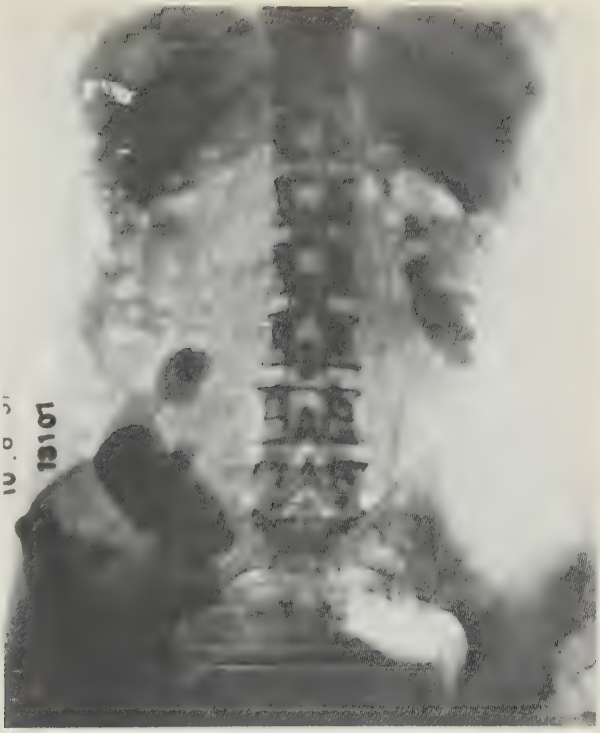


Figure 22. Intravenous urogram shows congenital dystopic nonrotated hydronephrotic left kidney. Note double ureter on right side.

Figure 23. Angiographic study in a case of extensive hypernephroma of kidney involvement.

Figure 24. Same patient as in Figure 23. Venous phase arteriogram demonstrates hypernephroma of renal vein.

Ray, etc.—have had wide application throughout the field of medicine. For example, their use for cerebral, cardiovascular, selective renal artery, and other local arterial angiographic examinations have made possible proper localization of lesions for exact surgical approach in their respective fields. These compounds, you will note, are derivatives of the original Hippuran and related to it in that the nucleus of all is the benzoic acid ring. These radiographic organic iodides have made excretion urography the cornerstone of urological diagnostic investigation, lending themselves to studies of the dynamics of the urinary system by cineroentgenography, and permitting important information to be obtained from the voiding cystourethrogram, and from nephrotomography. And the end, I hope, is not yet in sight.

ACKNOWLEDGMENTS

I wish to express my deep appreciation to the publishers, W. B. Saunders Co., for permission in utilizing material from the textbook *Urography* published in 1928 by Dr. William F. Braasch to whom I pay tribute.

I also wish to express my gratitude to the New York Academy of Medicine for utilizing the material in my Valentine Lectureship at the Academy of Medicine.

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Military Surgery: "Bullets and Blood Vessels"

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Man's inhumanity to man persists. This is emphasized repeatedly by armed conflict which exists, as verbal and recorded history will document, on any given day in some region of the world. Man's inhumanity to man is depicted in many ways. Figure 1 illustrates one method as painted by an unknown Flemish artist in the sixteenth century. Since the advent of gunpowder, however, man's ingenuity has concocted an armamentarium of destructive devices, many which exhibit an increasing and terrifying element of destructive capability during warfare.

History also emphasizes the persistent challenge that has faced military surgeons who must attempt to prevent unnecessary suffering and who must try to reconstruct the ravages of sophisticated modern weaponry as incurred on the many battlefields. Numerically, few military surgeons have been surgeons who have worked in this specialty area all of their professional careers. More often, civilian surgeons have responded to the increased need for medical support during a specific hostile situation. Often the accomplishments on the battlefield in caring for hundreds to thousands of injured young men have provided an opportunity to evaluate certain techniques within a relatively short period of time. The subsequent outcome has been the establishment of accepted principles of management of surgical problems which later can also be utilized under civilian conditions. History abounds with these accomplishments and is exemplified by the relatively recent experience during the Korean Conflict when military surgeons, led by Hughes, Jahnke, and Spencer, demonstrated for the first time that arterial repair could be routinely successful, even under battlefield conditions. One has only to reflect for a few moments to appreciate the many advancements that have occurred in this century and how many were directly related to experiences on the battlefield. In concert with the theme of the recent 200th anniversary of the United States of America, there is a painting at Fort Ticonderoga which exemplifies progress made in medicine during a similar period of time when one could question the "progress" that man has made in developing increasingly sophisticated weaponry (Fig. 2). Although "bite the bullet" is now used in a figurative sense, the destructive capability of high velocity bullets remains a problem with which the medical profession must contend, in the violence of urban conditions as well as on the battlefield.

With supersonic air travel, the world continues to "shrink" to the point where international exchange and cooperation are recognized as having increasing significance and importance. Use of the "dum-dum" bullet was outlawed for warfare in the Hague Convention of 1899. The well-known Geneva Convention of 1949 outlined additional rules and regulations on the battlefield in an attempt to prevent unnecessary and inhumane suffering. This work has recently been expanded under the auspices of the International Committee of the Red Cross. Military

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Figure 1. One of the many ramifications of man's inhumanity to man is depicted in the above painting. "Progress" made in developing weapons of increased sophistication and destructive capabilities has provided an increasing challenge for military surgeons. (Permission granted by the Rijksmuseum, Amsterdam, The Netherlands.)

surgeons suddenly find the perplexing challenge of being asked how warfare can be made more humane! What is inhumane or unnecessary suffering? Often the translation of these concepts is difficult from one language and one culture to another. I once replied to such a question at an international meeting with the following: "Even if I am shot in the buttock with a low velocity .22 caliber bullet, I would consider that the wound caused unnecessary suffering." How can military surgery interface with military tacticians, international diplomacy and international politics? These are some of the remaining questions that involve military surgery, the problem of managing wounds secondary to bullets, and the challenge of specific injuries such as those to the blood vessels. With this as some background, I would like to expand further on my 18 years of experience as a military surgeon. Although this was not a planned career, the professional challenge and stimulation has been formidable.

Training of the Military Surgeon

Immediately following World War II a residency program in surgery was established for military surgeons serving in military hospitals. Fully accredited programs were developed. My initial training and background as a military surgeon were at Letterman Army Hospital in the Presidio of San Francisco, California, which had served continuously as a military post since first established by the Spanish in 1775. After completing medical school at Stanford University School of Medicine (at that time part of the training was in San Francisco), I served a rotating internship at Tripler Army Hospital in Honolulu, Hawaii. With the doctor draft and a military service obligation, it seemed to be a reasonable alternative to spend this

Figure 2. "Bite the bullet." Approximately 200 years ago during the American War of Independence, round lead bullets were frequently placed between the teeth of a wounded soldier. Because pain medication was virtually unknown, the wounded soldier could bite into the lead bullet when he might otherwise have cried out with excruciating pain. (This is published with permission from the Curator of the Museum at Fort Ticonderoga, New York.)

period of my professional career in a training program. Returning to San Francisco for a residency in general surgery, I found that my teachers were outstanding military surgeons and that many consultants were my former professors from Stanford University.

The Army has great pride in its residency training programs in surgery which is justifiable. Outstanding teaching by dedicated military surgeons is augmented by the most outstanding consultants from the civilian academic world in medicine. This became obvious to me soon after completion of my residency when I had an opportunity to compare my training background with many other surgeons of my peer group when we served under less than ideal conditions in the Republic of South Vietnam.

Vietnam

After President Johnson's address to the nation on 28 July 1965, I found that I was one of a few young Army surgeons selected for a "sabbatical" in Southeast Asia. In 1965 there obviously were a great many uncertainties regarding the role of the United States Armed Forces in Southeast Asia. Rumor ran rampant and changed hourly. Similar to the Hollywood script for the World War II war movie, I found myself on board a crowded troop ship sailing for the South China Sea.

Time and space do not allow even a reasonable representation of the myriad of events and experiences that occurred which could fill a book, and maybe they should . . . someday. Anyway, it became very obvious to me while sitting on board the U.S.S. Simon Bolivar Buchner III that my background and knowledge of treating bullet wounds was minimal at best. True, I had some of the best teachers, both civilian and military, who had served in World War II and Korea. Nevertheless, it was apparent that experience would be the best teacher. The classic volume, *Wound Ballistics*,[5] published from the experience of the United States Army Medical Department during World War II and the Korean Conflict, became a valued reference. A professional manuscript of outstanding quality by Finck also provided valuable reference material.[10]

To say, however, that anyone can be prepared to face the ravages of war is ridiculous. The first patient that I was called to treat was a young soldier of a paramilitary group similar to a "home guard." He had sustained a high velocity gunshot wound of both thighs and had a partially severed right superficial femoral artery which had contributed to his hypovolemic shock by nearly complete exsanguination. At 0400 hours in a tent in the middle of the jungle in the Central Highlands of the Republic of South Vietnam in the heat and humidity associated with the monsoon season and with very limited logistical support, it is safe to say that conditions were far from ideal. The challenge continued when we were fully operational in our 2nd Surgical Hospital (MA), initially identical to the "MASH" of the Korean Conflict, except that conditions varied greatly from the script later to be popularized by Hollywood both in movie and television form.

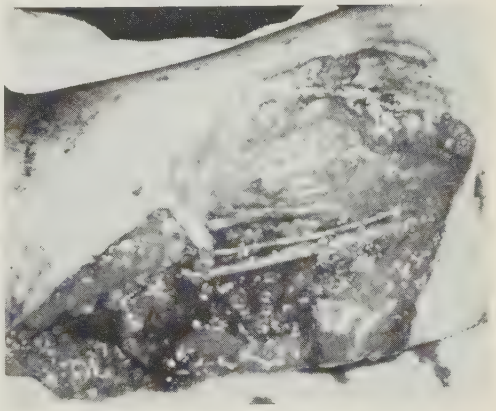

Figure 3. Massive soft tissue destruction in the right arm of a helicopter door gunner was caused by a high velocity .50 caliber missile. In addition to the brachial arterial trauma, there were also concomitant venous, osseous and nerve injuries. (*From* Rich, N. M., Baugh, J. H., and Hughes, C. W.: Acute arterial injuries in Vietnam: 1,000 cases. J. Trauma, *10*:359, 1970, with permission.)

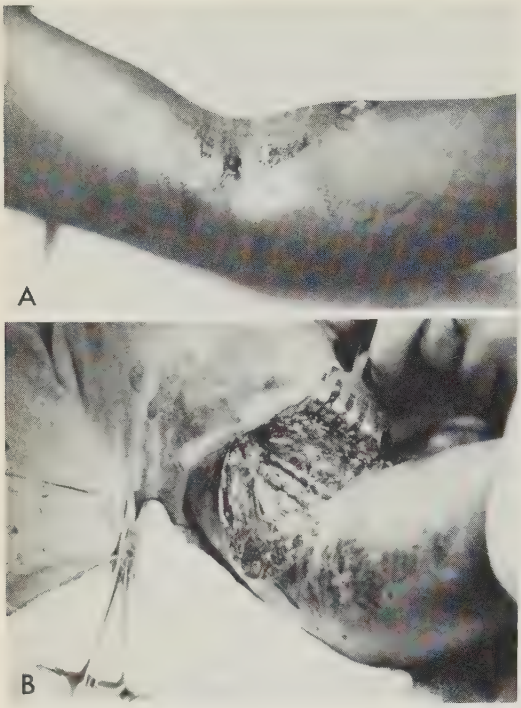

Figure 4. *A*, This low velocity gunshot wound of the antecubital area of the left upper extremity was caused by a .45 caliber bullet that went through and through twice as can be seen from the four circular defects all of approximately equal size of 1.5 cm in diameter. There is less tissue destruction as contrasted to the high velocity gunshot wound demonstrated in Figure 3. *B*, After minimal debridement, an end-to-end anastomosis of the left brachial artery was possible. A segmental interposition autogenous greater saphenous vein graft was required to restore continuity in the more extensive brachial arterial injury caused by the high velocity bullet shown in Figure 3. (*From* Rich, N. M.: Vascular trauma. SURG. CLIN. NORTH AM., 53:1367, 1973, with permission.)

One of our first patients demonstrated all of the ravages of warfare. This young American soldier had sustained a high velocity gunshot wound of the right upper extremity. In addition to massive loss of skin and soft tissue, there was disruption of the continuity of arterial flow in the left brachial artery, severe trauma to the median and ulnar nerves, concomitant venous trauma, and a comminuted fracture of the left humerus (Fig. 3). Many challenges existed in restoring arterial continuity utilizing an autogenous greater saphenous interposition vein graft in the brachial artery. It was also important to immobilize the fractured humerus which was accomplished by external immobilization. This was contrasted by an example of a lower velocity gunshot wound, also of the upper extremity (Fig. 4). The contrast between the massive tissue destruction of high velocity bullets and the more minimal wounding power of low velocity bullets is demonstrated and emphasized by these representative examples.

During a 12 month period (1965–1966), it was possible to specifically evaluate and study 750 combat casualties who sustained missile wounds. Early reports of this experience outline what more than 600 young American surgeons experienced during the involvement in Southeast Asia (1965–1972).[9, 15-20] Part of the study at the 2nd Surgical Hospital involved the cataloguing of all bullets and fragments (Fig. 5). The cooperative study included the expertise of personnel from Small Arms, Intelligence, Ordinance, and a number of other associated groups. The accuracy of being able to identify the specific wounding missile was felt to be in the range of 85 per cent. This helped to establish a better understanding for the wounding power of specific missiles and it was believed that patient care was thus enhanced.

Although a more extensive study was performed over a subsequent two year period of time by a larger complement with more extensive resources, this individual study from the 2nd Surgical Hospital remains valuable because of the detailed anaylsis and follow-up that were available and organized.

In addition to the major study of evaluating the wounding power of missiles in Vietnam, unusual, and even unique, situations developed. The question of the

Figure 5. One corner of the operating room theatre at the 2nd Surgical Hospital (An Khe, Republic of South Vietnam, 1966) was organized as a small medical museum. Of paramount importance was the study evaluating the wounding power of various missiles. Cards with bullets and fragments from various exploding devices were posted on the wall for comparison and future reference as depicted in this photograph (NMR).

value of acupuncture, prior to the later interest in this procedure in the United States, stimulated interesting exchange.[17] Also, the management of punji stick wounds provided irony in the days of modern conventional and atomic weapons. The primitive punji stick wounds often disabled the wounded soldier for as long a time as did many minor missile wounds.[51]

Experimental Wound Ballistics

Upon my return from Vietnam in late 1966, I was provided with an excellent opportunity to obtain long term follow-up of former combat casualties from Vietnam. My own specific interest in vascular surgery established the Vietnam Vascular Registry as a major project.[21] Now in the twelfth year of long term follow-up, we have been able to provide data of value for management of vascular trauma in the civilian setting. Representative of reports from our Registry effort are a number of references cited.[6, 12–14, 21, 23–49]

Based on the clinical experience in Southeast Asia, wound ballistics, the evaluation of the wounding power of various missiles, and the management of

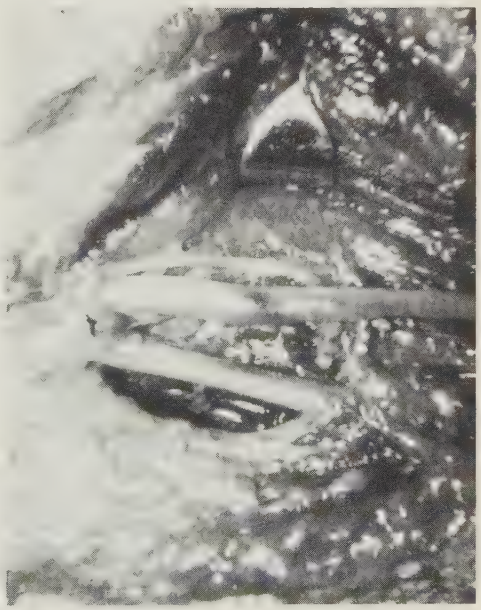

Figure 6. Contusion of the mid portion of the brachial artery, with the median nerve seen below, was caused by the temporary cavitational effect of a high velocity M-16 bullet. The absence of arterial flow beyond the contused segment can be appreciated by the smaller size of the artery *(right)*. The excised segment of the brachial artery demonstrated an area of minimal disruption with organized thrombus that occluded the lumen. (*From* Rich, N. M., Amato, J. J., and Billy, L. J.: Arterial thrombosis secondary to temporary cavitation. Surg. Dig., 6:12, 1971, with permission.)

injured arteries and veins were obviously related and equally important. An example is shown in Figure 6. The temporary cavitational effect, which can often approach 30 times the size of the residual cavity, of a high velocity bullet can cause thrombosis of an artery or fracture of a bone without the bullet actually striking these structures. Although previous experimental work had been performed,[5] and there were a few other interested investigators such as DeMuth[7, 8] and Finck,[10] we recognized that further investigation was warranted. New techniques in high speed photography provided more adequate visual documentation of the difference between high velocity and low velocity missiles.[1–4]

Vietnam Vascular Registry

The Vietnam Vascular Registry was established at Walter Reed Army Medical Center in 1966 to document and analyze the results of vascular repairs performed during the hostilities in Vietnam and to provide the long term follow-up of former Vietnam combat casualties.[21] With nearly 7,500 records of former wounded servicemen, this has become the largest collection of such data ever accumulated and duplication in the future is doubtful, unless a very controlled opportunity exists. Specific questions have been addressed such as the empiric recommendation during the Korean Conflict to routinely excise 1 cm of grossly appearing normal artery on either side of the obvious arterial trauma. In an evaluation of 116 arterial segments returned from Vietnam for review and study at the Armed Forces Institute of Pathology, however, it was demonstrated that success of the arterial repair could not be guaranteed by following this recommendation.[23] Because of this important study, it was generally agreed that excision of the grossly traumatized artery would be acceptable, despite the microscopic recognition of trauma in the area of grossly appearing normal artery. Experimentally, it was possible to demonstrate these changes up to a distance of 2 cm from the gross trauma when we turned to the experimental laboratory for confirmation.[1]

Through the Vietnam Vascular Registry specific problems have been addressed. An appropriate emphasis is given to the enigma of injury to the popliteal artery.[25, 26, 39, 44] There have also been systematic studies involving the subclavian artery,[37] the abdominal aorta,[6] and the common femoral artery.[41] The complications associated with arterial repair have been addressed.[28, 43] The problem of managing concomitant injuries such as associated fractures with vascular trauma have been evaluated.[32] Arteriovenous fistulas and false aneurysms have been included in an exhaustive review of 515 patients with 558 lesions.[42]

Of specific interest and worthy contribution to the management of injured patients has been the work associated with the recommendation for a more aggressive approach to the repair of injured veins.[27, 35, 38, 44, 45, 47]

Continuing in the theme of international exchange as previously outlined, some of these data have been published in French[30, 31] and in Spanish.[36] One of the most recent studies of an interesting and unusual problem, 22 patients who had missile emboli, has been reviewed.[48] Data from the Vietnam Vascular Registry have been included with a review of the surgical literature considering military and civilian experience throughout the world.[49]

Walter Reed Army Medical Center

Many of the contributions made by military surgeons to surgery in general have been documented and are appreciated, Walter Reed Army Medical Center holds the distinction of a well deserved world renowned reputation because of the number of contributions that have been made by military surgeons during their service in Walter Reed General Hospital. The associated Walter Reed Army Institute of Research and the Armed Forces Institute of Pathology provide the opportunity for experimental corroboration with clinical impressions.

In 1966 a fellowship training program in peripheral vascular surgery was established at Walter Reed Army Medical Center. Ranking as one of the early programs of its kind, there has been an opportunity to provide additional expertise in vascular surgery for general surgeons who remain in the Army residency training program. The opportunity and stimulation for increased academic productivity have been obvious by recent contributions to the literature.

Military surgeons have hosted a Seminar in Vascular Surgery for the past five years. This has provided a most important exchange between outstanding civilian

surgeons with an interest in vascular surgery and their counterparts in military surgery.

By an act of Congress in 1972, the Uniformed Services University of the Health Sciences was established. Walter Reed Army Medical Center, Bethesda National Naval Medical Center, and Malcolm Grow Air Force Medical Center are the three major teaching hospitals of this new University. With a strong civilian basic science faculty and outstanding military surgeons, this represents a unique opportunity to ensure that civilian and military surgery will continue the important exchange and mutual professional stimulation. The increased academic credibility of military medicine, and military surgery in particular, because of the new University, should be obvious. Many military surgeons look upon this new University as the one possible salvation of a strong military Medical Department, particularly in a time of peace, when military medicine historically is at its lowest ebb. The first two classes of young medical students in uniform represent the future for military surgery. Only through a combined civilian and military effort will these students receive appropriate training and be prepared to function as adequate military surgeons.

The International Military Surgeon

Medicine is a universal language. Mutual concern for patient welfare transcends political and religious idiologies. A military surgeon frequently serves as an international statesman. This is becoming an increasingly important role for military surgeons.

In an editorial, "Weapons and Wounds," written in 1975, details of the Conference of Government Experts on the Use of Certain Conventional Weapons were briefly summarized.[40] This meeting was held in Luzerne, Switzerland, from 24 September to 18 October 1974 under the auspices of the International Committee of the Red Cross. The Conference was designed to continue the thoughts and goals originated by the 1949 Geneva Convention in an attempt to eliminate unnecessary and inhumane suffering during the time of armed conflict.

Military surgeons from many nations have contributed to the recent increased interest in the wounding power of missiles. Much of this has been well summarized by Scott of the Royal Army Medical Corps of the United Kingdom.[50] Swedish leadership in the experimental evaluation of wound ballistics has been championed in the past few years by Rybeck and associates. Western nations, the Eastern bloc, and the nonaligned Third World Nations have struggled with the problems of attempting to control, and hopefully eliminate, the increasing use of sophisticated arms. The working paper for the Conference mentioned above was organized in March 1974 by Egypt, Mexico, Norway, Sudan, Sweden, Switzerland, and Yugoslavia. To the nearly 50 nations that were represented at the Luzerne Conference later in 1974 were added Austria, Belgium, Canada, Cuba, Finland, France, Indonesia, Italy, New Zealand, Spain, United Kingdom, USA, USSR, and West Germany.

As a military surgeon, with a particular interest in wound ballistics, I served on two occasions in 1974 and 1977 as a Faculty Opponent for Göteborg University against two Swedish surgeons who selected aspects of this subject of wound ballistics as the topic for their theses.

Conclusion

The challenge continues! The need for enthusiastic young surgeons in military surgery is great. The military surgeon is called upon to be outstanding in surgery, in experimental research, in military tactics, and in international diplomacy. For me, the professional challenge has been formidable as it had been for military surgeons before me and will be for those who will follow. Hopefully, the challenge will continue to be met.

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Thermal Burns: A Personal Odyssey

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THE BOSTON YEARS

It was early in 1942, not long after Pearl Harbor Day, that Dr. Charles Lund, Associate Professor of Surgery at the Harvard Medical School, told me that he had been asked by the Office of Scientific Research and Development to organize a Burn Research Service at the Boston City Hospital, that this was considered by the Government to be of the highest priority for the war effort, and that Dr. Cecil Drinker, Professor of Physiology at the Harvard School of Public Health had recommended me as resident and research fellow for the Burn Research Service. I was then a surgical intern at the Beth Israel Hospital in Boston.

To backtrack a bit, I had gone to the Boston Latin School and from there to Harvard College where Dr. George Hitchings was my tutor. Dr. Hitchings invited me to work at the Huntington Memorial Laboratory. This was a remarkable opportunity because in addition to Dr. Hitchings there was a bevy of exceptionally talented investigators and an air of excitement and challenge pervaded the laboratory. My studies dealt with reducing substances, especially vitamin C, in tumor tissues, and thus began my life-long interest in ascorbic acid.

I continued to work in Dr. Hitchings' laboratory throughout college and during my first 3 years at Harvard Medical School on various aspects of ascorbic acid, e.g., the kinetics of its oxidation and reduction. I decided to spend most of my fourth year working on the chemical composition of lung lymph with Dr. Cecil Drinker. However, by the time I started working with him in 1940, he was asked by the Office of Scientific Research to develop an oxygen mask for use by the Air Force. Our efforts were successful and the mask we developed was used for the first time by the U.S. Air Force in General Doolittle's assault on Tokyo.

I was impressed by Dr. Lund's vision, imagination, vigor, and organizational ability and joined the Burn Research Service in November, 1942. I was appointed also a Research Fellow in Medicine at the Thorndike Memorial Laboratory. The Burn Service had already begun, Dr. George Clowes serving as the first resident. Five days after my arrival, the Coconut Grove fire occurred. This was (and still is) the largest civilian disaster in the United States. That night over 550 patients, mainly young men and women, were brought to the Boston City Hospital; 132 living patients were admitted to surgical and medical wards in many different buildings. Plasma and albumin were in very short supply; isotonic saline was the major replacement fluid. Triple dye, which had been introduced by Aldrich, who was then at the Boston City Hospital, was the local treatment used for most patients. The great majority of the patients had severe respiratory tract injury. This posed major problems since in the early 1940's, the sophisticated cardiorespiratory support currently available was not available, nor were antibi-

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otics. Drs. Finland, Davidson, and I made rounds continuously primarily (but not exclusively) checking respiratory tract function and for possible pulmonary infection—it took about 6 hours just to see each patient once. Drs. Lund, Clowes, John Byrne, Newton Browder, and others oversaw the fluid and local burn wound therapy. Close communication among the various physicians existed. Along with the best possible clinical care we could provide, a wide variety of studies were carried out and continued in subsequent years with other burn patients, along with experimental studies in the laboratory, as reflected in the 50 to 60 papers dealing with burns published by our group between 1943 and 1948.

Our investigations spanned a wide front—local treatment, nylon-backed split thickness skin grafts, the use of dry rather than bland ointment, pressure dressings, and the use of promptly applied close-fitting plaster casts for hand and wrist burns, based on experimental work of Glenn and Drinker (with Ross Green who joined me as resident on the Burn Service), shock, including the demonstration of fibrinolysis (Tagnon), renal failure, respiratory tract injury (a classic monograph was published with Finland as the senior author and C. S. Davidson as a major collaborator),[2] wound healing, thrombocytopenia, anemia (Ham and Shen), and metabolic and nutritional problems.[4] The latter included demonstrations of the marked decrease in urinary nitrogen excretion, disturbances in plasma amino acid and carbohydrate metabolism, rapid depletion of the water-soluble vitamins,[18] and consequent increased caloric, vitamin, and protein requirements by severely burned patients. We described the occurrence of Addison's disease in a severely burned woman.

Lund and Browder designed a chart for the recording and calculating of the area of body surface burned, a method which is universally used today.

During my five years at the Boston City Hospital, I had joint appointments in medicine and surgery; in surgery, first as resident and research fellow on the Burn Research Service and later as resident in General Surgery; in medicine, as research fellow in Medicine at the Thorndike Memorial Laboratory. During my fourth year, I took 6 months off to study at MIT to learn about radioisotopes. I then conducted a number of in vitro and in vivo investigations of phosphorus metabolism using ^{32}P; these were among the first such studies.[6]

THE CHICAGO YEARS

In the fall of 1947, I joined the U.S. Army Medical Nutrition Laboratory in Chicago as Chief of the Radiobiology Division and the University of Illinois School of Medicine as Assistant Professor of Surgery. Our experimental animal work centered around the influence of thermal burns and anemia on wound healing,[7] the role of ascorbic acid on the maintenance of reparative collagen and the reversion of healing wounds to an immature state, and the metabolic response to injury, including the effect of thermal injury on protein and electrolyte metabolism and influence of exogenous testosterone propionate on these metabolic factors.

A major study was the investigation of whether the increase in urinary nitrogen excretion after extensive thermal injury represented increased protein catabolism or decreased protein anabolism, which tissues were involved, and to what extent.[11] For these, the first such studies conducted, ^{15}N glycine was used. The data showed that the rates at which the tracer amino acid was incorporated into various tissue proteins were similiar in burned and unburned animals, but that the rates in the most actively metabolizing organs (e.g., liver, gastrointestinal tract, pancreas) were higher in the burned rats. There was no evidence of decreased protein synthesis in any organs. Although carcass (skeletal muscle and bone) protein turned over slowly, its mass gradually decreased and accounted for almost all the increase in urinary nitrogen excretion. In contrast, total protein contents of the metabolically very active organs such as the liver increased in the burned rats, although these organs turned over protein more rapidly than normal. Although the period of negative nitrogen balance after injury is commonly called the catabolic response, the term is inaccurate. Both anabolic and catabolic processes go on after severe injury, but all tissues do not participate equally in the response. Thus, catabolism predominates in the carcass, anabolism in the liver.

At this time, I wrote a review article with Dr. Lund on burns for Disease-a-Month. Colonel William S. Stone, then Commandant-in-Charge of the U.S. Army Research and Development Office, read the article and suggested that I move to the Medical College of Virginia where the Army was supporting the burn research of Dr. Idris Evans. My associates and I were to remain administratively with the Department of the Army. It seemed to me that this was a good opportunity, and I agreed. Dr. Evans was an imaginative and contemplative surgeon and the ambiance was exciting.

THE RICHMOND YEARS

My investigative work at the Medical College of Virginia continued to be both experimental and clinical and centered about metabolic and nutritional problems associated with thermal burns, with emphasis on our attempts to determine optimal calorie:nitrogen ratios and optimal carbohydrate:fat ratios for patients of varying ages, sex, and severity of injury, and at various times after injury, effects of immobilization and calisthenic exercises on the metabolic responses of the sick and injured (with Edith Vail) and wound healing. We demonstrated that the previously healthy severely burned man (20 to 50 years of age) required about 3 to 4 grams of protein and 60 calories per kg body weight, that the previously healthy severely burned woman of comparable age required about 2 to 3 grams of protein and about 50 calories per kg body weight, and that seriously burned children would remain in good nutritional state if given a diet from the start similar in calorie and protein content to that required by healthy children of comparable age, a finding corroborated later by Sutherland and her colleagues in Scotland. We found also that brief periods of calisthenic exercises of the uninjured extremities of young men with femoral fractures reduced significantly the intensity and duration of the period of increased urinary nitrogen excretion (all the fracture patients received a dietary intake of 1½ gram protein and 45 calories per kg of body weight), the reduction being mathematically equivalent to the loss found by Whedon and Schorr when young men were immobilized in ankle to axilla plaster spicas.

Some of our clinical investigative studies centered around the metabolic fate of infused erythrocytes, bone marrow function, red cell survival, and nitrogen balance following transfusion polycythemia in normal young men.[5] These studies were carried out while I was at the Army Medical Nutrition Laboratory in 1947–1949 and were conducted because physicians were recommending that repeated transfusions of blood or packed red blood cells be given to undernourished, but not anemic, patients for nutritional purposes. We found that when normal men were made polycythemic by transfusion, both donor and recipient cells were destroyed at a normal rate. Erythropoiesis was depressed; the degree of depression was directly related to the quantity of red cells infused; almost complete cessation of red cell synthesis followed an increase of the red cell mass by 40 per cent. A slow steady excretion of 0.5 to 1.0 grams of urinary nitrogen per day (above the control "equilibrium" value) began shortly after the infusions and continued for about a month. The total cumulative "extra" nitrogen excreted was equal mathematically to about 80 per cent of the nitrogen content of the infused erythrocytes. Calculations based on the observed survival of the infused erythrocytes and the patient's own erythrocytes and production of new erythrocytes showed, however, that the greater part of the "extra" urinary nitrogen could be accounted for by nitrogen from amino acids diverted from normal erythropoiesis proportionate to the level of polycythemia.

At the Medical College of Virginia, we extended these studies to patients in the early and late periods after injury. Young men with femoral fractures, previously healthy, were studied. They were on fixed diets providing 1.5 grams of protein and 45 calories per kg body weight per day. After several days, when they were demonstrably in negative nitrogen balance, they were transfused with fresh red blood cells. In no instance was erythrocyte survival shortened. We then studied patients who were malnourished, but stable, following severe burns or illness. In no instance was survival of the patient's own red blood cells or of the infused red blood cells shortened. This included a patient purposefully made markedly polycythemic.

In 1952, I went to Korea to study problems of amino acid and protein metabolism, nutrition, wound healing, and infection following battle injuries, especially in soldiers with renal failure. There were remarkably rapid increases in tissue protein breakdown and serum urea nitrogen and potassium concentrations in these patients. Weight losses were extreme, would healing was slow, and wound infections were frequent and severe. Although plasma urea concentrations were as much as 30 times normal in the patients with renal failure, total free plasma amino acid nitrogen concentrations were near normal.[9]

At no time were all the amino acids depressed or elevated. Rather, they grouped themselves as follows: (a) glycine, histidine, threonine, proline, and glutamic acid stayed near normal; (b) leucine, isoleucine, lysine, valine, tyrosine, and alanine rose moderately during the first week and fell; and (c) phenylalanine, aspartic acid, and methionine also rose during the first week, but to a greater degree. Taurine bore little or no relation to the other amino acids. At times, it was very high. We had earlier found plasma taurine very high in burned rats.

In all plasmas analyzed, a heterogenous amino conjugate was found. This was the first time this component had been described in patients. We had earlier discovered such an amino conjugate in severely burned rats. The amino acid composition of this conjugate fraction varied from patient to patient, and in the same patient from day to day.

Following extracorporeal dialysis the total free amino acid nitrogen concentrations were unchanged. Generally, the levels of the individual amino acids were nearer normal at the end of dialysis than at the beginning. The plasma amino conjugate, like urea, fell sharply after dialysis. John Howard was Chief of the U.S. Army Surgical Research team in Korea at the time, and William Meroney and later Paul Teschan headed the Renal Dialysis Team.

THE WASHINGTON YEARS

By the time of my return from Korea, new laboratories had been constructed at the Walter Reed Army Institute of Research in Washington, D.C. I moved there in 1953 and remained there for the next 8 years. The support provided me by the three Commanding Officers, Colonel William S. Stone, General John Wood, and Colonel Richard Mason, and Directors of Surgery, Colonels (but now Generals) Carl Hughes, William Moncrief, Thomas Whelan, and Colonel Edwin Pulaski was phenomenal.

My investigations related to thermal burns during this period continued in the areas of metabolism, nutrition, wound healing, shock, and infection. We showed, for example, that the biochemical scurvy which Lund, Johnson, Green, and I had described in burned patients 15 years earlier reflected physiologic scurvy as assessed by wound healing,[10] that liver regeneration occurred faster than normal in severely burned rats, in contrast to the impaired healing of laparotomy wounds, as we had postulated from our earlier studies of tissue protein turnover studies with ^{15}N glycine. We detailed further the behavior of plasma amino acids and the plasma amino conjugates in patients with burns, injury, and liver failure, including the effects of hemodialysis. In the 1950's concern of possible future nuclear warfare was at a peak, so we had begun studies of whole body radiation and whole body radiation and thermal injury; we found a striking synergistic potentiation between the two.

In other studies, Harold Upjohn, Morton Creditor, and I determined the metabolic effects of intravenous fat emulsions, including its protein-sparing action in normal men[22] and the occasional severe complications of hepatomegaly, splenomegaly, anemia, thrombocytopenia, jaundice, and fever.

In 1954, I went to Korea again, this time to study the metabolic, physiologic, and nutritional problems of patients with acute hemorrhagic fever. This is a disease of viral origin which in its acute phase is characterized by massive interstitial edema, especially retroperitoneal, resulting in markedly decreased plasma volume and shock, remarkably similiar to burn shock. Renal failure was a frequent complication and adrenal insufficiency occurred occasionally in those severely affected. These patients showed many metabolic and hormonal derangements similar to those shown by seriously injured patients.[8]

In the wound healing field, Alex Kessler, Hyman Rosen and I were the first to chromatograph collagen into what later was recognized as the α and β chains.[3] With Erving Geever, Rosen, Leo Crowley, Upjohn, Costain Berard and Arthur Steer, a number of studies of wound healing in normal, injured (traumatic, including burns, irradiation) and metabolically and nutritionally abnormal animals (e.g., deuterium oxide fed rats, scorbutic guinea pigs) were carried out, and with Geever and William Moncrief the healing of skin incisions in normal male volunteers was studied as the basis for future studies in injured patients.

Because of the Army's policy of centralizing patient burn care at the Brooke Army Medical Center, I was not directly involved in the care of burn patients during my years at Walter Reed except in a consultant role, notably at the Medical College of Virginia where I continued to collaborate actively with B. W. Haynes in the burn investigative work.

While at Walter Reed, much of my attention with Ole Malm, Bud Tennant, Erving Geever, Richard Horowitz, and Leo Crowley was directed toward exploration of the use of germ-free animals and animals with defined microflora in the studies of shock, growth, metabolism, nutrition, wound healing, and endotoxemia. A consequence of these studies was the beginning of our attempts to apply the techniques of the germfree laboratory to problems of patient care in the operating room and on the wards. William Moncrief, Marie LaConte, and Edwin Pulaski of Walter Reed and P. C. Trexler of Notre Dame collaborated in these studies.

THE NEW YORK YEARS

In July 1961, I moved to the Albert Einstein College of Medicine. The decision to leave Walter Reed was a very difficult one for me since I had such strong research support and freedom of action there and so many good friends and colleagues. However, the opportunity to help build a new medical school which in just a few short years had already demonstrated clear-cut potential for greatness, the desire to get back to teaching medical students and once more to be closely involved in the study and care of patients on a continuing basis, and the air of excitement and enthusiasm that permeated the Einstein, finally led me to decide to come to New York. Drs. David State, Robert Frater, and Marvin Gliedman, as Chairmen of the Department of Surgery, have been of enormous support, and I am indebted to them for the opportunities provided me and my associates.

At the Einstein, my associates and I have been involved in both experimental animal and clinical studies dealing with burns and closely related problems. The U.S. Army Medical Research and Development Command and the National Institutes of Health have supported our work generously. We were able to set up in 1962 a General Clinical Research Center—Acute. The Unit was interdisciplinary in character—I was Co-Principal Investigator and Program Director. I relinquished the latter position after a few years to Louis DelGuercio, who along with Rita McConn and John Siegel carried out a number of pioneering imaginative and exciting studies. After a number of years, the New York City Health and Hospital Corporation took over the support of the Unit and it became our Surgical Intensive Care—Burn Unit. By that time, Dr. DelGuercio had left and I resumed Directorship of the Unit and relinquished the position of Chief of the Burn Service to Dr. John Stein who had received his general surgical residency training with us, during which time he had spent a year as an NIH Research Fellow working on wound healing with me; we were the first to demonstrate that the polymorphonuclear leukocytes played no direct role in the healing of skin incisions. An active, interdisciplinary Burn Service has been forged at the Jacobi Hospital.

In collaboration with Arnold Nagler, I have been conducting studies for years of hemorrhagic and traumatic shock. In particular, emphasis has been placed on circulating cardiovascular toxic factor(s). The basic aim of our investigations has been to isolate, characterize, and determine the role of the toxic factor(s) in experimental and human shock syndromes and to investigate ways of preventing its appearance or enhancing its detoxification. Several years ago, we corroborated Fine's and Nagler and Zweifach's observations of a passively transferable lethal factor (PTLF) in the blood of animals suffering from severe protracted traumatic and hemorrhagic shock. We then demonstrated that germ-free rats also show the

passively transferable lethal factor (PTLF) in their blood and plasma after severe, prolonged hemorrhagic shock. We also demonstrated PTLF in patients suffering from severe shock—hemorrhagic, septic, myocardial.

PTLF is lethal when injected into recipient animals, demonstrating a remarkable cardiac toxicity. It is our hypothesis that during severe shock, stagnation and hypoxia secondary to compensatory ischemia cause an alteration in plasma protein(s) to form a "pretoxin" (CVTF-precursor); subsequently, upon perfusion of the lymphoid tissues (primarily the spleen) following transfusion of the patient or animal, white blood cell enzymes enter the circulation to cause the activation of the "pretoxin" to the CVTF (cardiovascular toxic factor). Acid phosphatase, an enzyme released from white blood cells is capable, in vitro, of converting PTLF (cardiotoxin precursor) from animals and patients to the potent cardiotoxin. Eli Seifter has collaborated in this phase of the studies. The CVTF (bound) migrates electrophoretically with gamma globulin and behaves as aggregated (bound) gamma globulin upon ultra-centrifugation and has the immunospecificity of gamma globulin. It is relatively heat-stable, and nondialyzable; a chromatographically pure preparation is colorless, soluble in water and alcohols, and is non-TCA precipitable.[19]

One of my continuing investigational interests has been directed toward improviding the wound healing of severely injured patients, including those with extensive burns. Our studies have fallen into three general areas:[14]

1. Attempts to ameliorate the adverse effects of serious injury on wound healing by various nutritional, chemical, and hormonal means, singly and in combination, with emphasis on reparative vessel formation, fibroblastic proliferation, collagen synthesis, and collagen cross-linking.

2. The demonstration, isolation, and chemical identification of possible humoral stimulators and regulators of wound repair and liver regeneration.

3. Since wound healing and wound infection are so closely interrelated, studies directed toward the prevention and control of wound infection and its local and systemic effects have been carried out. In particular, these have included attempts to improve by various chemical and hormonal means the depressed local and systemic resistance to infection associated with serious injury.

Some *representative findings of the studies in Category I* follow:

Wound healing is impaired significantly after unilateral or bilateral femoral fracture of rats, just as we have found previously to be the case after thermal burns.

Transferring rats with femoral fracture to a room with a temperature of 30°C as compared to a room at 22°C lessens the negative nitrogen balance and mitigates the impaired wound healing compared with similarly maintained wounded rats without fracture.

Testosterone propionate reduces the intensity and duration of the negative nitrogen balance following femoral fracture of rats, but does not ameliorate the impaired wound healing at a room temperature of 22° or 30°C.

Supplemental vitamin A accelerates wound healing of normal rats as assessed by the gain of strength of skin incisions in the formation of reparative collagen in subcutaneous implanted polyvinyl alcohol sponges.

Supplemental vitamin A ameliorates the impaired healing of skin incisions and formation of reparative tissue in subcutaneous implanted polyvinyl alcohol sponges of rats with femoral fracture, but not of open skin wounds of such rats.[20]

Supplemental vitamin A increases experimentally induced intraabdominal adhesions while Citral, a vitamin A antagonist, lessens them.

Supplemental arginine increases the healing of skin incisions and the formation of reparative tissue in subcutaneous implanted polyvinyl alcohol sponges in normal rats. This effect of arginine is not seen in hypophysectomized rats which have been supplementd with ACTH, thyroxine, testosterone propionate at maintenance levels, and growth hormone at maintenance and above maintenance levels.

Strain-specific fibroblasts, cultured in vitro, implanted into subcutaneous polyvinyl alcohol sponge implants increased the rate at which reparative collagen was formed. Such fibroblasts, cultured in vitro, appeared unchanged morphologically after eight subcultures, but when implanted in rats, all rats after 1 year developed sarcomas which were readily transplanted to other rats.

We have been interested in the problem of *liver regeneration in relation to*

wound healing and injury especially burns for some time. Conceptually, the liver regenerative process from some points of view, is similar to that of a healing wound: (1) What initiates the healing and regenerative processes? (2) What keeps them going? (3) What stops them? While at the Walter Reed Army Research Institute, we found, as mentioned, that while the healing of skin incisions is impaired in rats with severe burns, liver regeneration following partial hepatectomy is accelerated in such rats. These physiologic data correlated with studies of protein synthesis and breakdown which we conducted using N^{15} glycine in these animals. Achilles Demetriou has carried out much of this work and Eli Seifter, Benjamin Thysen, and Michael Gatz have collaborated with us.

There is convincing evidence that an hepatotropic factor(s) appears in the sera of rats and humans after partial hepatectomy.[1] The results of our initial fractionation experiments show that the hepatotropic factor (assessed by the in vitro growth of E_1 cells derived from rat foetal livers) present in serum following partial hepatectomy is ultrafiltrable and has a MW of 5,000 to 12,000. Preliminary experiments showed that the in vitro cell growth stimulating activity is not lost following incubation in the presence of RNase, DNase, and trypsin.

Several investigators have presented data suggesting that insulin and possibly glucagon are the chief hepatotropic factor(s). Our experiments showed that sera of rats and dogs which underwent pagtial hepatectomy after prior pancreatectomy stimulate in vitro growth of E_1 cells to the same extent as sera from nonpancreatectomized rats and dogs which have undergone partial hepatectomy. To investigate this further, the effects of sera of rats 24 hours following 68 per cent partial hepatectomy or sham hepatectomy on hepatocyte growth in vitro were tested (a) directly, (b) after treatment with insulin-specific antibody, and (c) after treatment with charcoal which binds both immunoreactive insulin and glucagon. The hepatocytes were obtained from adult rats and grown in primary monolayer cultures. The data showed that the in vitro hepatotropic activity of serum of rats after partial hepatectomy is unaffected by (a) selective removal of insulin, or (b) by removal of insulin and glucagon.

We also studied the effect of conditioned media on hepatocyte growth. Conditioned media is media in which hepatocytes from livers of normal rats or rats which have undergone sham hepatectomy or partial hepatectomy have been grown for varying times; the hepatocytes are removed, and the respective media then used for culture of normal hepatocytes. Medium conditioned by hepatocytes from regenerating liver stimulated the in vitro growth of hepatocytes, but media conditioned by hepatocytes from normal or sham-hepatectomized rats did not, suggesting that regenerating liver is a source (direct or indirect) of an hepatotropic factor(s).[21]

Sepsis local and systemic continues to be a major problem of seriously *burned patients.* My associates and I have attempted to *devise methods for prevention of infection of burn patients by two complementary approaches:* (1) rapid removal of the irreparably damaged skin of deep burns which, so long as it is present is highly susceptible to infection, and (2) prevention of cross-contamination and cross-infection, since the evidence is clear that contamination of the burn patient by "hospital" organisms is a major etiologic factor in sepsis of burn patients. For the rapid removal of the burn eschar we have used two experimental and clinical approaches: (1) *the use of the CO_2 laser* and (2) *chemical, enzymatic and nonenzymatic debridement.* Both are directed toward the prompt removal of irreversibly damaged burned tissue in ways which avoid the major blood loss when the ordinary "cold" surgical scalpel is used and which will, at the same time, not have systemic or local toxicity and will permit immediate or very prompt skin grafting. For the prevention of cross-contamination, we have applied the techniques of the germ-free laboratory, using plastic isolators.

Norman Levine, Stanley Stellar, Ralph Ger, and John Stein collaborated in studies of the use of the CO_2 laser.[17] The CO_2 laser was used first by us for the excision of third degree burns in pigs, with a significant reduction in blood loss when compared to cold-knife excisions of comparable areas. Autografts applied to a freshly lased surface showed excellent "takes" and persist in a normal fashion. There was no evidence of local or systemic toxicity due to the use of the laser in removing burn eschars of up to 15 per cent body surface area.

Our experience with patients demonstrated a significant reduction in blood loss when the laser was used to excise third degree burns compared to cold-knife

excision of comparable burns in the same patients. The "take" of a skin graft immediately applied on the freshly lased surfaces was comparable to that obtained on the surgically excised areas. A drawback was the relative slowness of the CO_2 laser which we initially used (American Optical). A later model with higher power from Israel was significantly faster, but it was the initial production model and relatively unstable.

Levine, Salisbury, Pruitt and associates, and Fidler, MacMillan and associates have shown that the currently commercially available CO_2 lasers have no major advantage over the bovie for excision of deep burns. In my view, there will be developments in the laser field, such as being pursued in Seattle with a combination argon-quartz scalpel, which have the potential to be of significant technical importance and to offer significant advantages for the excision of extensive deep burns. A theoretical advantage of the laser over ordinary scalpel excision is that the laser seals off small blood vessels and lymphatics and kills microorganisms at the line of excision, factors which may help in minimizing the bacteremia that often occurs following surgical scalpel excision of deep burns.

Seifter, Kan, Gruber, Levine, Crowley, Al Watford, and I have been working on the *chemical debridement of burns* for several years.[15] Chemical debridement offers the potential of requiring no anesthesia, requires no differentiation of depth of burn by the surgeon, and entails minimal blood loss. Necessary attributes are that it be rapid, that its action can be controlled, and that it has no local or systemic toxicity. The chemicals used should permit concomitant use of local chemotherapeutic agents. Our experiments show that Bromelain derived from pineapple-stem is a particularly effective agent which appears to meet the requirements just mentioned. Third degree burn eschar involving 5 to 40 per cent of the body surface of pigs and rats can be removed in hours after a single application. The eschar is generally not solubilized but the interface between the nonviable burned skin and the underlying viable tissue is affected in a way which permits the very rapid blunt dissection (e.g., with a wooden throat stick) of the burn eschar with very little blood loss and no damage to the underlying tissue. Rats may be grafted successfully immediately; the subcutaneous layer of the pig is too avascular to accept a graft immediately but the wound may be covered temporarily and grafted later. Partial thickness burns and unburned skin do not appear to be damaged. Rats and pigs so treated, including those with very large burns, survive, grow, and show no evidence of systemic toxicity as judged by a number of laboratory and chemical parameters.

Commercial Bromelain is a mixture of various enzymes and other chemicals, many of which are inert in terms of debriding activities. We have been fractionating commercial Bromelain by physical-chemical techniques, isolating and concentrating component(s) having proteolytic activity, as judged by standard protein hydrolysis techniques and by vitro and in vivo assays with burn and unburned skin. We have isolated the main proteolytic component(s) and have prepared it in a sterile form; it is active in debriding burn skin rapidly without evidence of toxicity. We are fractionating Bromelain now to obtain the component(s) with mucolytic activity, which we believe play a major role in the debriding activity of Bromelain, enabling it to act at the interface between the viable and nonviable tissue, so that the eschar can be removed readily without waiting for fragmentation or solubilization of the eschar. We are attempting to isolate the proteolytic and mucolytic fractions so that they can be characterized chemically and obtained reproducibly, desirable characteristics for future application.

Experiments have also been conducted using other chemical agents, chiefly nonenzymatic, alone and in conjunction with enzymatic agents; some results indicate synergistic activities are possible. Also, it is possible to include certain antimicrobial agents in the chemical debridement preparations without any interference of activity of one with the other. Other experiments in our laboratory have shown that prompt excision of the deep burn and wound coverage reduce infection dramatically, not only when the wound is contaminated initially directly with virulent bacteria, e.g., *Ps. aeruginosa* but also when the purposeful contamination is initiated systemically (intravenously) and secondarily involves the burn wound. Levine, Pruitt and associates have reported similar findings using intraperitoneal *Ps. aeruginosa* as the bacterial challenge. Comparable experiments using *rapid*

chemical debridement have been conducted in our laboratory. These were undertaken with the view that rapid (hours) debridement accomplished by the combined use of chemical debriding and local chemotherapeutic agents will obviate the possibility of any increase in infection, caused by the use of relatively slow chemical debridement, as reported for Paraenzyme and Travase. Our experiments support our hypothesis since we have found that the results of the rapid chemical debridement and prompt wound coverage are comparable to surgical excision and wound coverage. It is possible also that the short-term use of systemic antibiotics begun just before and continued during, and for a short time after, the rapid chemical debridement may prove useful for the prevention of infection, as is the case for abdominal operations of the clean-contaminated and contaminated types.

Complementary to these methods for the rapid removal of the burn eschar are our attempts to prevent cross-contamination of the burned patient. Conceptually, *physical barrier isolation* is a logical solution to the problem of cross-contamination and cross-infection, since some transfer is required before colonization and infection resulting from exogenous microorganisms are possible.

The use of isolators automates aseptic techniques and offers a reliability and simplicity not possible by conventional medical and nursing isolation techniques. The feasibility of applying this approach to man was apparent to Trexler and me in 1957 immediately after Trexler and Reynolds introduced flexible transparent plastic film animal isolators. The central feature of our program was the development of isolators for: (1) performance of operations in a closed environment to include exogenous contamination; (2) isolation of patients usually susceptible to infection; and (3) isolation of patients with serious infections. An extension of these is the containment within an isolator of only part of the patient, e.g., an extremity. The use of these isolators is integrated into the total care programs for the patients.[12]

Our first operations were carried out at the Walter Reed Army Hospital, but the bulk of our experience has been at the Albert Einstein College of Medicine. We have found that even the most complicated types of abdominal surgery can be carried out with ease from the surgeons', anesthesiologists', and nurses' point of view. The data indicate that the ingress of exogenous bacteria and fungi during operation can be prevented by the isolator technique. The wound infection rates among the patients undergoing clean-contaminated operations in two groups of comparable patients undergoing operations by the isolator or conventional techniques were 3.5 per cent and 9.4 per cent respectively. Seymour Alpert, Theodore Salzman, P. C. Trexler, Peter Kranz, Majorie LaDuke, Maureen Dinerman, Catherine Sullivan, Dolores McCaffrey, and Mary Johnson collaborated in these studies.

The extension of the flexible film isolator technique to the care of patients on the ward was undertaken simultaneously with its application to the operating room. Many of the logistical problems are similar in the two types of applications but the medical and nursing problems are much more involved and prolonged in the former and the method has to be psychologically acceptable to the patients and their families.

Our experience with patients—some suffering from very severe burns, some undergoing renal transplants, some with drug-induced agranulocytosis—cared for in whole-body and/or partial-body isolators indicates that the required medical and nursing care can be carried out with little difficulty.[13]

The data show that the ingress of exogenous microorganisms can be prevented. Others, notably Burke and his associates, who have the largest single experience with burned patients, Hummel, MacMillan, Altemeier and their colleagues, Haynes and Hench, and Lowbury and colleagues, have reported similar findings.

The possibility of buildup of microorganisms within an isolator has been raised. This can be prevented largely by appropriate ventilation and washing of the interior of the isolator. Also, for certain patients, such as those with extensive deep burns, who are kept in isolators for many weeks or months, periodic transfer of the patient to another isolator is practical.

The chief source of contamination of the burns of patients treated in isolators seems to be from the patients' gastrointestinal tract, a finding also of Haynes and Hench, Hummel, MacMillan, Altemeier and associates, Lowbury and colleagues, and Burke and his associates. An approach to this problem used with seeming

benefit in an initial study by Larkin, Moylan and Balish is the use of oral antibacterial and antifungal agents to "near-sterilize" the gastrointestinal tract of burned patients treated in laminar air flow units combined with conventional reverse isolation techniques (gowns, masks, gloves, etc.).

Pari passu with these clinical studies we have conducted a series of *investigations in the germ-free animal laboratory* to investigate relationships between the animal host and its indigenous microflora in regard to a number of fundamental biologic and medical problems, with particular emphasis on mammalian metabolism and nutrition,[16] the development of chemically defined diets, trauma (including burns) and irradiation, wound healing, immunologic problems, infection, and shock. Eli Seifter, Dorinne Kan Gruber, Charles Gruber, Erving Geever, Al Watford, Ernst Jaffe, Floyd Doft, Llewellyn Ashburn, Leo Crowley, Arnold Nagler, and Komei Nakao have collaborated in these studies.

EPILOGUE

During the 35 years I have been working with burns, there have been many important advances which have derived from laboratory and clinical research intimately tied to patient care, teaching, and private and governmental action. I cannot attempt even a tabulation of these because of space limitation but I would like to mention a few.

During the years 1943 to 1946, Cecil Drinker and William Glenn carried out imaginative experimental studies of the effects of burns on lymph flow at the Harvard School of Public Health and Oliver Cope, Francis D. Moore, and their colleagues carried out their classic studies on the victims of the Coconut Grove fire who were admitted to the Massachusetts General Hospital and subsequently on other burn patients and also conducted experimental studies on lymph flow after burns (Cope), early excision of deep burns (Cope and Langohr), changes in fluids, electrolytes, other metabolites, and body composition in patients with serious burns and other injuries and illnesses (Moore). At the same time, Jacob Fine, Howard Frank, Arnold Seligman, Alexander Rutenberg, and Edward Frank were carrying out their exciting studies on shock at the Beth Israel Hospital. These studies laid the basis for much of our understanding of the shock syndrome(s) and endotoxemia.

It was also while I was at the Boston City Hospital that Sanford Rosenthal and Herbert Tabor at the National Institutes of Health began their classic studies with rodents, demonstrating the critical role of sodium replacement for the prevention and therapy of burn shock. Later, their colleagues, Carl McMillan and Kehl Markley, extended these studies in imaginative fashions, including investigations of burn sepsis. Mention must be made of the carefully conducted prospective randomized study carried out in Peru under the guidance of Rosenthal and Markley of the relative effectiveness of sodium chloride and plasma in the prevention and therapy of burn shock.

Cope and Langohr and Harvey Stuart Allen practiced, and urged, the early excision of deep burns. Edward Howes was attempting to accomplish this by enzymatic debridement. Topical chemotherapy of traumatic wounds and burns was studied by Frank Meleny, William Altemeier, and Edwin Pulaski, but the data did not support this practice.

Sir David Cuthbertson had begun his classic observations of the metabolic disturbances after injury and Francis D. Moore had begun his notable studies of surgical metabolism which have so influenced our understanding and care of seriously ill and injured patients. Isidor Ravdin, Jonathan Rhoads, and Harry Vars were carrying out studies of nutrition, wound healing, and liver function; and Paul Cannon and his colleagues were conducting their experimental studies of amino acids, proteins, and resistance to infection, with emphasis on humoral antibodies. Robert Elman was working with intravenous protein hydrolysates, Charles Davidson with intravenous synthetic amino acids, and Fred Stare and Robert Geyer with intravenous fat emulsions. William Abbott, Carl Moyer, and Charles Fox made important observations regarding fluid and electrolyte problems of burned patients, and John Kinney and his associates have done much to clarify our understanding of

the metabolic disturbances after injury, particularly changes in energy metabolism. Calvin Long's studies of carbohydrate and protein metabolism are notable, as are those of John Border, Rapier McMenamy, and George Blackburn. The major contributions in this field of Wilmore, Mason, and Pruitt of the Army Surgical Research Unit are mentioned later. A major contribution to nutritional prophylaxis and therapy was the introduction of present day parenteral hyperalimentation by Jonathan Rhoads, Stanley Dudrick, Harry Vars, and Douglas Wilmore.

The psychologic problems faced by severely burned patients and their families was recognized and studies carried out in several centers.

There had been two other major fire disasters in the United States during the 1940's: the Hartford Circus Fire in Hartford, Connecticut, and the oilfield disaster in Galveston, Texas. It was at the latter that Truman Blocker took charge in such an effective fashion and set standards for superb clinical care during a very active career for the next quarter century. Virginia Blocker, John Lynch, and Steve Lewis played major roles in much of this work.

Alistair Wallace of Scotland introduced the exposure treatment of burns in the 1950's, and the Burn Group at the Birmingham Accident Hospital in England (Leonard Colebrook, Douglas Jackson, Lowbury, Michael Sevitt, John Davies) began their important contributions in many aspects of the burn problem, including local treatment, burn excision, and microbiologic and pathologic studies.

It was while I was in Richmond that Evans devised his formula for fluid replacement. B. W. Haynes, Jr., became head of the Burn Service there in 1954 and pioneered a number of important burn studies.

It was in 1947 that the U.S. Army Surgical Research Unit at Fort Sam Houston started. The Unit reached its zenith under the leadership of Curtis Artz, John Moncrief, and the present Commanding Officer, Basil Pruitt. This has been the single most influential Burn Center. The clinical care provided and the experimental and clinical studies carried out have been outstanding and have covered almost every aspect of burns, ranging from local therapy, e.g., the use of Sulfamylon and prompt excision of deep burns, fluid and electrolyte therapy, respiratory tract injury, infection, metabolic disturbances and their pathogenesis, nutritional prophylaxis and therapy, morphologic changes, and psychiatric and other rehabilitative problems. In addition to Artz, Moncrief, and Pruitt, mention should be made of Arthur Mason, Douglas Wilmore, Robert Lindbergh, John Davis, Charles Baxter, Wesley Alexander, William Curreri, and Elinor Pearson, among many others. "Graduates" of the SRU are the Chiefs of a large number of major Burn Centers in the United States, e.g., Bruce MacMillan, Duane Larson, Bruce Zawicki, Charles Baxter, William Curreri, Paul Silverstein, Roger Salisbury, John Stein, and Norman Levine.

An important development about 15 years ago was the decision of the Shriners to support three major Burn Centers—at Galveston (Duane Larsen), Cincinnati (Bruce MacMillan), and Boston (John Burke). Each is conducting outstanding basic and clinical investigations and providing superb medical care. A major contribution of the Galveston Group has been the use of pressure dressings to prevent and/or reverse hypertrophic scars; a major contribution of the Cincinnati Group has been clarification of some of the effects of burns on the resistance of patients to injection and the interrelationship between such resistance and nutrition; a major contribution of the Boston Group has been the use of immunosuppression, and prompt excision of very extensive deep burns, autografting and homografting, and maintenance of patients in rigidly controlled protected environments.

Irving Feller at the University of Michigan has spear-headed the collection and analysis of data regarding the occurrence, therapy, and outcome of burn injuries in the U.S. Charles Baxter, Tom Shires, and William Curreri studied a variety of problems at the Parkland Hospital in Dallas, notably early fluid and electrolyte disturbances, circulating myocardial depressent factors, nutritional prophylaxis and therapy, and the use of subeschar injections of antibiotics in patients with burn wound sepsis.

Carl Moyer's and William Monafo's introduction of the use of 0.5 per cent $AgNO_3$ dressings has had a major effect on combating burn wound sepsis and lessening the extent of water vaporization from the burned surface, a feature which Fred Caldwell and Moyer had studied. Caldwell went on to make a number of

contributions in the area of temperature regulation, including specific relevance to burns. Fox had introduced silver sulfadiazine for local therapy and Monafo has recently introduced a new silver salt of cerium for the local treatment of burns, which appears to be especially effective as an antimicrobial agent, and Caldwell and Monafo have been studying the use of hypertonic saline for resuscitation.

There are a number of other investigations in the U.S. and other countries and my failing to specifically mention them is due only to lack of space and is not to be construed as any indication that their contributions are not of major importance. Patently this is not the case. Consider the introduction of tangential excision by Janzekovic and the warm air and early excision regimen of Liljedahl, the metabolic and nutritional studies of Wilkinson, and the clinical contributions of Dogo.

The formation of national and international burn societies has been important for the stimulation of interest in burn problems. A major effort in burn prevention has been mounted; George Crikelair and Ann Phillips Crocker have been especially active.

In the research areas, in the U.S., the Army Medical Research and Development Command (Colonel Walter Scheetz) and the Institute of General Medical Sciences of the National Institutes of Health (Dr. Emily Black) have been especially supportive. It is creative, imaginative, carefully conducted basic and clinical research that will lay the foundation for significant advances. Looking ahead, if the homograft rejection phenomenon can be solved, if improved methods for the early excision of deep burns are devised, if our understanding of, and methods for care of respiratory tract injury consequent to thermal (smoke, noxious, fumes, etc.) injury improves, we can look forward to significant decreases in morbidity and mortality. It may be possible to lessen the severity of the burn injury consequent to the thermal insult if methods can be devided to increase local and systemic resistance to heat, goals which are, I believe, achievable. Finally, great "salvage" will come from vigorous programs in education and burn prevention.

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A Personal Memoir: Plastic Surgery in the Twentieth Century

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This paper is not intended to be a complete history of twentieth century plastic surgery, but rather a personal viewpoint detailing my own experience and the opportunity I had to participate in the development of plastic surgery in the twentieth century.

There is an erroneous but widespread popular belief that plastic surgery originated in World War I. This idea was, of course, not true, for plastic surgery, or what is known as plastic surgery, had, like surgery in general, its origins in antiquity. The earliest record of plastic surgery appears to be in Susruta—a basic text of Hindu medicine. Most scholars agree that it is impossible to date the work of the author accurately, but have come to accept the date as the fourth century A.D., although they assumed that the text was probably originally written in the sixth century B.C., including practices that then were of antique tradition.

Throughout the years that followed there were from time to time various writings on particular specialized subjects. In 1556 Pierre Franco published his "Petit Traite" in which he included the first description of a surgical repair for a congenital cleft lip. In 1597, Gaspare Tagliacozzi published his "De curatorum chirurgia per insitionem." This is the first book on plastic surgery, an historic landmark in surgical annals. This well illustrated work shows the classic picture of the patient with his arm brought up to his face and a flap extending from the arm to the nose—a procedure for the restoration of a lost nose by an arm flap (the so-called Italian flap). This procedure is still being utilized today except the flap used today is a tubed pedicle rather than an open flap which Tagliacozzi used. J. C. Carpue reported in 1816 (London, Longman) an account of two successful operations using the so-called Indian flap for restoring a lost nose from the integument of the forehead. This method is still used today. Throughout the latter part of the nineteenth century many article appeared on various subjects such as skin grafting and transplantation of other tissues. It was not until some years later that the first comprehensive textbook appeared.

In the early twentieth century, two French textbooks on plastic surgery appeared, both by Nelaton and Ombredanne—the first one titled "La Rhinoplastie" (1904) and "Les Autoplasties" (1907). This latter book dealt with the plastic repair of various areas of the body.

World War I (1914–1918) brought forth an avalanche of cases which stimulated what might be called the "rebirth of plastic surgery," although, by regulation in the United States Army, plastic surgery was limited to the maxillofacial area. Plastic surgery in Britain in World War I started about January 1916 at the Cambridge Hospital, Aldershott. Later, a rapid increase in the scope of the work led to the removal of the hospital to Sidcup, where Major Gillies, later Sir Harold Gillies (Fig. 1), was joined by colleagues from among the British and allied forces. A number of these were later to hold prominent academic positions; e.g., Pomfret Kilner, who

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Figure 1. Sir Harold D. Gillies of London, father of British plastic surgery.

subsequently became Professor at Oxford, and Kazanjian who became Professor of Plastic Surgery at Harvard. John Staige Davis' book, "Plastic Surgery," issued in 1919, was the first general comprehensive modern textbook on plastic surgery published in the English language and in 1920, Gillies' book "Plastic Surgery of the Face," an account of his war time experience was published.

Colonel Blair (Fig. 2), Medical Corp U. S. Army, returned from Sidcup after the war to found the Plastic Surgery Department of Washington University School of Medicine. Here a team came together whose work in skin grafting was outstanding. This is but one example of the American surgeon returning back and continuing to contribute and develop his skill in plastic surgery in the post-war years. Blair also wrote extensively on injuries and treatment of diseases of the jaws. His classic book "Surgery and Diseases of the Mouth" was first published in 1912 and reissued several times.

After World War I, a group of American and Canadian plastic surgeons who had served in World War I formed the American Association of Oral and Plastic Surgeons. This was the first plastic surgery society in the world. In 1941, it was renamed the American Association of Plastic Surgeons. Later I was to be invited to become a member. Subsequently, societies were formed in Britain, France, Germany, Japan, and other countries.

In 1931 in the United States, largely through the driving efforts of the late Jacques Maliniac, a second plastic surgery society was formed, called The Society of Plastic and Reconstructive Surgery. This society rapidly increased in size. The name of this organization was subsequently changed to The American Society of Plastic and Reconstructive Surgeons. The American Cleft Palate Association was formed in 1943.

Important developments in plastic surgery occurred in the first half of this century. An example of this is the invention of the tube pedicle. Priority for this must be given to Vladimir Petrovich Filatov, a Russian ophthalmologic surgeon working in Odessa during World War I. He reported on the tube pedicle in the Vestnik Opthalmologii April-May 1917, and at that time had the vision to foresee many of its applications. In 1939, in Surgery, Gynecology and Obstetrics (69:779–793), Earl Padget, M.D., and Hood, an engineer, described the dermatome and its use. Their paper is called "The Calibrated Skin Graft—A New Principle and New

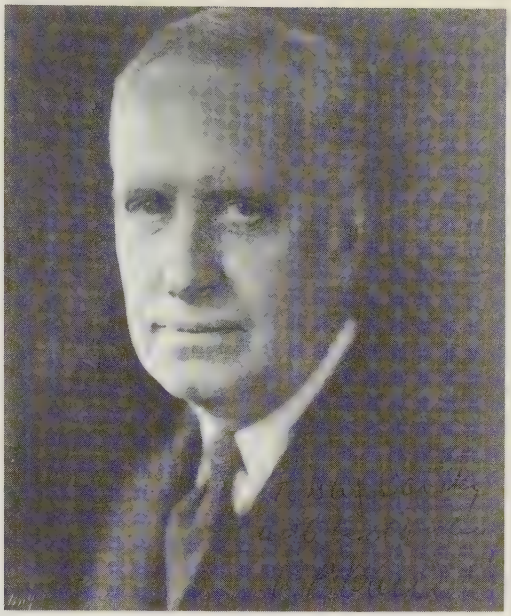

Figure 2. Vilray P. Blair, M.D., one of the great leaders in American plastic surgery.

Type of Graft." This instrument made it possible for an unskilled surgeon to cut large sheets of graft, for once he mastered the principle, it required very little skill and facilitated skin grafting of large areas. In the years that followed, a great many different kinds of mechanical skin grafting devices were developed, most of them either driven by electricity or by compressed air. They all tended to simplify the technique of cutting a skin graft.

Several landmark papers in plastic surgery deserve special notice. One by Blair and Brown appeared in Surgery, Gynecology, and Obstetrics, July 1929 (*14*:82–97). This article was titled "The Use and Uses of Large Split Skin Grafts of Intermediate Thickness." They detailed the method of cutting and applying them. The skin was stretched taut by a suction box held in the surgeon's left hand, while countertraction was made in back of the surgeon's knife, a large, flat, extremely sharp knife. The graft was cut by a to-and-fro shaving motion at a depth determined by the surgeon. This required a certain amount of skill. Blair and Brown did not, of course, invent the split skin graft, but they made an enormous contribution and helped popularize its use on a wide scale.

Blair and Brown in 1930 wrote another extremely important paper (Surgery, Gynecology and Obstetrics, July 1930, Vol. L1, 81–08), "Mirault Operation for Single Harelip." This was one of the first articles that gave a detailed description of the surgical repair based on sound principles and experience. For many years it was the "standby" for many surgeons.

I have often been asked "Why did you go in for plastic surgery?" The field was not well known and vaguely defined, with few training opportunities in the United States. My father was a physician, an internist, who practiced in New York and had achieved prominence. I must say at this time that my father's intense interest and devotion to his profession was, I believe, one of the main reasons why I went into medicine. I knew, even before I entered professional school, that I intended to do maxillofacial surgery. I thought the best plan to prepare myself was to acquire a dental degree first, since a good deal of jaw surgery would be involved. Following this, I intended to go to medical school and thereafter to obtain training in the field of plastic surgery.

I was fortunate, indeed, to begin my career at a particularly auspicious time. I had the occasion to know many of the great leaders in this specialty, most of whom had been engaged in military service in World War I, and then later, to meet those

who were engaged in World War II in which I myself served, and to have participated in some especially interesting projects after World War II. I have seen the development of plastic surgery from its modest beginning, witnessed its growth into a genuine specialty, and then recently, have seen a trend by many away from reconstructive surgery toward a concentration on lucrative cosmetic surgery, so-called "esthetic surgery," in order to give it a better sounding name. "A rose by any other name. . . ."

I took my premedical work at the University of Pennsylvania and while at the University of Pennsylvania School of Dentistry I came in close contact with the late George M. Dorrance and Robert H. Ivy who were in charge of the Department of Maxillofacial Surgery. In the early twenties, Major Gillies (later Sir Harold Gillies) paid a visit to the United States and spoke at the University of Pennsylvania. Dorrance introduced me to him. The surgery of repair fascinated me and I looked forward from that time on to the opportunity of working with Gillies. It was to be some time before I was able to do so.

I graduated in medicine in 1926 from New York Medical College, and from 1927 to 1934 I trained in the surgical department of the New York Postgraduate Medical School and Hospital, at that time affiliated with Columbia University where J. Eastman Sheehan was in charge of plastic surgery. In 1934 Dr. Sheehan suggested that I go to England to Sir Harold Gillies and arranged a fellowship for me.

Gillies had a certain genius for plastic surgery, a very agile mind, and was quick to take up rather novel ideas. I recall once when we were operating at a nursing home in London, he was preparing to graft a burn case and I saw him walk over to the sister in the operating theater and whisper something to her. She left, she returned, opened the lid of the water sterilizer (they had water instrument sterilizers in those days), and threw something heavy inside. The lid closed with a clang and the water boiled furiously. Shortly thereafter she came out holding a tray for the theater sister who picked up, of all things, an ordinary meat grinder.

Meanwhile, Gillies had cut a split skin graft, which he took and placed into the cooled meat grinder and quite calmly ground up the graft. I made no remark on this rather strange procedure, but I could see Gillies looking at me sideways waiting for me to ask questions. I refused to bite. Meat grinders in the operating room were, by my manner, or seemed to be, a regular occurrence. After Gillies ground up the graft he took out the small pieces and spread them over the granulating area. He was not especially careful to see whether or not the cut surface was in contact with the granulating area. I had the unpleasant impression that it was all done for its effect on a young American surgeon. It puzzled me, for I was sure that Gillies knew, even as I did at that time, that the graft would not take. Sure enough, several days later when it came to uncover the graft, very few of the tiny pieces had taken. Why had Gillies gone to such trouble to make an impression on a young stranger?

Ivan W. Magill was Gillies' anesthesiologist at that time. Magill had introduced endotracheal anesthesia, also nasal intubation. This gave complete control of the airway and facilitated surgery about the face. Magill was a superb anesthetist. Observing him do an endonasal intubation was like watching a magician perform a sleight of hand maneuver. He had his own machine which he set, and maintained a smooth anesthesia. At one hospital he had an upholstered chair with a slip cover and a stack of Punch magazines which he read. Occasionally he would leave the operating room—so sure was he of his machine. I suspect this was for effect, for he was observing his patient from a distance.

I remained good friends with Gillies over the years, and we saw each other from time to time in London and America. A rather amusing incident occurred years later in Cali, Colombia. We were both elected honorary members of the Colombian Plastic Surgery Society. At a seminar on cleft lip, Sir Harold presented a rather bizarre idea. He turned to me and said, "Arthur, what do you think of it?" Not much, I thought, but I hesitated for a split second, and then sweetly replied, "Sir Harold, when the nightingale sings, all other birds remain silent."

Pomfret Kilner had by this time (1934) split with Gillies (having previously been a partner) and was now on his own, although they had rooms in the London Clinic, 149 Harley Street. From the very first moment I met Kilner, I liked him and we became fast friends. Although it is more than 40 years since I met Kilner, I

remember quite clearly it was a winter afternoon, a Friday. He was a little late in returning to his rooms in the London Clinic where I waited for him. He came in a somewhat roly-poly man who smiled and greeted me with warmth and friendliness. We chatted for some hours as the winter evening darkened. I came, a young stranger, and I left that night, a friend, for from the beginning we were good friends. This lasted throughout his lifetime. He taught me a great deal and I always thought of him as my professional father.

After finishing my fellowship, I returned to New York late in 1934 where I worked as Sheehan's assistant at New York Polyclinic and Medical School. During the years from 1935 to 1939 I had the privilege of spending a good deal of time at various clinics, particularly Blair's in St. Louis, and also with Kazanjian in Boston.

I gave considerable thought to the publication of an American journal of plastic surgery and discussed the matter with the late Dr. John Staige Davis, who was in favor of the idea and encouraged me in going ahead with it. Accordingly, in early 1939 I took the matter up with the publishers, Williams and Wilkins of Baltimore. In February 13, 1939, they advised me that the launching of a periodical in this field would be a losing proposition for quite a few years to come. Their letter concluded, "Naturally, the idea is yours and it is understood that we shall not undertake any periodical which might be competitive." Several years later, while I was in the military service, Dr. Staige Davis, in a letter to me, wrote he had heard that Williams and Wilkins *were* publishing a journal for the American Society of Plastic and Reconstructive Surgery. It appeared in 1946. No excuse was ever offered for the reversal of their decision. Years later I was to become an associate editor of the journal.

Toward the end of the 1930's, Vilray Blair, John Staige Davis, George Dorrance, and others were working on the formation of the American Board of Plastic Surgery. It was at first a subsidiary of the American Board of General Surgery but soon became an independent board. I was fortunate in receiving an invitation to become a founding member. Years later as a member of the Board, I found my role as Chairman of the Residency Review Committee worthwhile for it made it possible to regulate and help the training programs to maintain high standards.

In 1939 World War II broke out in Europe but it was not until December 1941 (after the Japanese attack on Pearl Harbor) that the United States entered the war. I volunteered for military duty and was sent to Harvard, Massachusetts General Hospital, to take a course in Plastic Surgery under Dr. V. H. Kazanjian, where the textbook I had written in 1938 was the textbook for the course.

There was a great shortage of hand surgeons and the army planned to set up in the Zone of the Interior—which is the United States mainland—nine centers for plastic surgery and for hand surgery. I was assigned to the Center for Plastic and Hand Surgery for the Fourth Service Command in Tuscaloosa, Alabama. Here, after the African campaign began, we had an avalanche of hand injuries which were very complicated. These cases required not only resurfacing, but frequently had nerve injuries, muscle and tendon defects, as well as bone loss, besides in many instances severe functional loss.

After the war in 1946, The American Society for Surgery of the Hand was organized, consisting of about 28 hand surgeons from the military, and a number of civilians, a total of about 35 members. It was a tremendous stimulus and impetus in the development of surgery of the hand, and inspired the formation of societies for surgery of the hand in various countries of the world. Those engaged in hand surgery came from three specialties: plastic surgery, orthopedic surgery, and general surgery. In 1976 it had grown to 340 members, I served as President in 1965.

The post-war years were busy and exciting ones. Besides practicing, teaching, and attending meetings, I found time to set up a tissue culture laboratory. I also wrote a number of books—"Principles of Plastic Surgery" in 1950 and "Congenital Anomalies of the Hand and their Surgical Treatment" in 1958. Training programs were expanding, many new journals were burgeoning (splendid ones) such as the British Journal of Plastic Surgery, The Scandinavian Journal, and others.

In the early fifties I was invited to join the staff of the Mt. Sinai Hospital in New York City, and to organize a teaching and training program in plastic surgery, which I thought a great challenge. We were able to set up a good training program, a hand clinic, and the first approved cleft lip and cleft palate center in New York. It

was at the Mt. Sinai Hospital that the "Hiroshima Maidens" project was carried out in 1955 and 1956.

In 1965, I left Mt. Sinai Hospital to become full time Professor of Plastic Surgery at the Albert Einstein College of Medicine in the Bronx, New York. Here I organized a successful teaching and training program, which is still in existence. It was from this base that I carried out the Children's Plastic and Reconstructive Surgery project in Saigon, South Vietnam.

INTERNATIONAL PROJECTS—HIROSHIMA

On the morning of August 6th, 1945, during World War II, a single bomb, fission type uranium 235U, 20 Kilotrons, was dropped on the city of Hiroshima, Japan, at that time headquarters of The Second General Army. The bomb exploded at 1800 feet over the heart of the city. In the resulting explosion 70,000 people were killed or missing and 70,000 were injured. The area of total destruction measured about four square miles. From sixty to ninety thousand buildings in an area of nine and a half square miles were destroyed or badly damaged. Thus World War II ended and the world entered the atomic age.

Even at a distance of 4,000 feet, the temperature exceeded 1000° centigrade. There were, as is usual with atomic explosions, both blast injuries and nuclear radiation injuries; two-thirds of the fatalities died of burns on the first day. About 50 per cent of all deaths were due to burns of one kind or another; many of those injured by blast were also burned. During the first week more deaths occurred from burns than from any other type of injury.

Some of the burns were due to flame of clothing either set afire by the initial blast or from subsequent conflagration. The overwhelming majority of burns of those who survived were those of the flash type. This is the result of a huge quantity of radiant energy acting at effective intensity for an exceedingly short interval, approximately three seconds. It has been estimated that at least 90 to 95 per cent of the burns were of the flash variety—the result of thermal radiation—and only 5 per cent due to flame. Flash burns were fatal up to 6,000 feet, a little over a mile for unprotected or unshielded individuals in the open. Even clothing provided some measure of protection. Light clothing provided better protection than dark clothing.

It is at once obvious that the possibility of treating mass casualties of such severity and so great a number presents insurmountable difficulties. It is our carefully considered opinion that there does not exist anywhere in the world today sufficient trained personnel, facilities, materials, and supplies to properly treat the staggering number of casualties that would occur in the atomic bombing of any large congested city where a population cannot be protected.

In 1955, 10 years after the Hiroshima bombing, I was asked by Mr. Norman Cousins, editor of the Saturday Review and chairman of the Hiroshima Peace Center Associates, to go to Japan to examine the patients and to prepare a report. We planned to do so and were to be accompanied by an internist, Dr. William Hitzig.

The other two members of the mission preceded me to Japan, and when I arrived there several days later and deplaned, I was met by a barrage of television lights, reporters, and newsreel photographers. From the very day of the bombing, there was an enormous amount of interest and emotionalism.

During all this, I never heard a single remark from the Japanese about how terrible it was to bomb without any warning the United States fleet in Pearl Harbor and to entomb American sailors in capsized vessels to die the slow death of asphyxiation. My service in the Medical Corps of the United States Army in World War II (and later my experience in Vietnam from 1967 to 1975) left me with a deep and enduring impression of the utter tragedy of war, its horrors, miseries, and almost incomprehensible suffering, and in the end, all too often—the sheer futility.

The Japanese press, especially the anti-American press, took great advantage of the situation (our presence), and simply could not understand why Americans would be sent to examine the patients injured in the bombing and to arrange for future treatment. Philanthropy at that time simply did not exist in Japan and many of the Japanese reporters found the situation incomprehensible. We were followed constantly and subjected to a nonstop barrage of questions. When it came to

examining the young girls, the Japanese reporters wished to be present in order to make sure that nothing untoward was going on. This I refused to permit, and we made a compromise. Patients were examined behind a screen where the Japanese newspaper people and television people could hear what was going on, but they could not see the disrobed young women.

During the examinations Japanese nurses were present at all times, of course, and we were assisted by several Japanese doctors who subsequently came to America with us. The situation remained touchy for several days until at a press conference I lined up a group of Japanese reporters and radio men before my own camera, took their pictures, and said it was now my turn to question them. This seemed to break the ice and from that point on our relations improved immeasurably (Fig. 3).

Our final plan, after examining all the patients that we could, was to select a group of approximately 25 young women who were most in need of surgery, bring them to the United States together with Japanese surgeons, and carry out both the treatment of the girls and help to train the Japanese surgeons in this specialty.

At the time of the original examination, we were struck by the fact that most of the injuries were on the left side, and upon questioning the patients found that most of them had been facing toward the blast, having been about 1500 meters or about a mile from hypo center. At first examination it became apparent that the disfigurements were scars varying from thin, plastic, mobile scars to dense, heavy pigmented keloids. Although questioning revealed the fact that many of the patients had suffered from initial radiation illness, the lesions present were scars and contractures, the result of thermal burns. There was no evidence at that time or in subsequent examination of biopsy material that the lesions themselves were radiation injuries. These findings confirmed the well known fact that atomic explosion injuries are due to *heat, radiation,* and *blast.*

Of the group examined, 44 per cent had only a single injury, while 56 per cent had injuries of the face, neck, and hands or some other part of the body. On occasions when there were injuries in two areas, it was possible to operate on the same person with two teams, thus saving considerable time.

It was believed at one time that keloid formation might be due to the gamma rays of nuclear radiation, but there was no evidence to support this view. There is no

Figure 3. The surgeon "breaks the ice" by becoming the photographer, Hiroshima, Japan, 1955.

question that keloid formation was stimulated by secondary infection, the ever present complication of slowly healing burns. No doubt there were further complicating factors in the production of scar and keloid formation due to the large number of casualties and the difficulties of early treatment. Contamination and irritation of slowly healing burns were causative factors. Malnutrition, too, may have played a part. Perhaps a very important contributing factor is the Japanese racial characteristic toward keloid formation.

Three of the problems we encountered in addition to the actual surgical repair, which was often very difficult, were keloids, hypertrophic scar formation, and hyperpigmentation of grafts; in some instances, there was difficulty in finding a proper donor site for a free graft.

The Japanese agreed with us that the best plan would be to take the patients to New York where they could be treated at Mt. Sinai Hospital. The surgery was to be performed by me and my two associates, Dr. Sidney Kahn and Dr. Bernard E. Simon, assisted by several teams of Japanese surgeons. The first team consisted of Dr. Goro Ouchi and Dr. Tomin Harada. This team was succeeded several months later by Dr. Masakazu Fukuu and Dr. Sadam Takahashi.

We brought with us to the United States an older Japanese-American woman, Helen Yokayama, a superb character, a woman of sympathy, understanding and great intelligence. She not only acted as "den mother," confidante, and chaperone, but was an important factor in keeping the girls in a high state of morale. Between operations the girls lived with Quaker families. Very close personal relationships were established with the patients and also with the Japanese doctors, and to this day, some 20 years later, we still carry on a correspondence and are visited from time to time by our patients and the doctors.

After about a year of treatment, the girls returned to Hiroshima and further treatment, if necessary, was to be carried out by the Japanese doctors who had helped us in New York.

As a result of our activities, we were able to set up three plastic surgery fellowships for Japanese doctors, and three surgeons subsequently came to the United States, completed the course, and three of them are now serving as teachers on the academic staffs of the Universities of Nagasaki in Tokyo and Hiroshima.

An interesting sidelight is the fact that the Japanese passed two laws. One law was that the wage earner of a family, if he had to undergo surgery as a result of atomic bombing, would be subsidized by the government, and the second was that the patients themselves who had been injured in the atomic bombing could be subsidized.

Looking back, it seems to me that it was necessary for us to exert a great deal of tact and consideration and kindness, and these qualities overcame the initial hostility which we faced with various groups: the newspaper men who were suspicious, the public who did not understand philanthropy, and the professional groups in the city and elsewhere who felt that they might lose face by having their patients taken care of by foreigners. We were indeed fortunate to be able to overcome these fears.

The Japanese surgeons proved to be excellent students who developed first rate techniques. It is very gratifying to know they soon formed a Japanese Plastic Surgery Society, followed by a Journal for Plastic Surgery, and are engaged in a great deal of research. I had the distinction of being the first honorary member of the Japan Plastic Surgery Society—a distinction which I treasure greatly.

One of our students, Dr. Onitzuka, has written one of the first textbooks in Japanese on plastic surgery.

THE VIETNAM PROJECT

Like all thoughtful people I was deeply troubled by the Vietnam war. We seemed to have gotten ourselves involved deeper and deeper—there seemed to be no avenue open to peace; casualties kept increasing and there seemed to be an endless saga of death and destruction.

During the turbulent sixties when the war was going badly and a storm of distrust, dissension, and disorder swept over our country and reaped a harvest of

anger, bitterness, and violence, it was frightening. Then came the profoundly disturbing reports of thousands of war-injured children in Vietnam. It seemed that we had truly reached "the winter of our discontent." Our Hiroshima experience had impressed us deeply for we knew that the children were the tragic, innocent victims of war who carry for a lifetime the physical scars and psychic trauma. It was at this point in time and mood that a Chinese proverb came to mind. "It is better to light a candle than to curse the darkness." Something had to be done! It was at this time that I was approached by a young New York attorney, T. R. Miller. We pondered over what could be done to help the children of Vietnam. We then organized Children's Medical Relief International Incorporated, and decided that the first thing to do would be to send a survey team to Vietnam to determine the actual conditions.

Accordingly, in February 1967, I led a survey team to Vietnam, and with the consent of the American and Vietnamese authorities, we started at Hue near the demilitarized zone, and journeyed southward surveying hospitals and other health facilities, trying to get a sound estimate of the number and type of casualties in children and what facilities were available for treatment, and whether there were any trained specialists able to do so.

In general, at that time, conditions in Vietnam were the same as in all other Southeast Asian countries: tuberculosis, smallpox, cholera, typhoid, typhus, plague, malaria, poliomyelitis, protein malnutrition, gastrointestinal parasitism as high as 100 per cent in some areas, and leprosy endemic in certain places; 50 per cent of the children died before reaching the age of five years. I shall not horrify you by going into great detail about the condition of the children. We did indeed find many war-injured children and many desperately in need of surgery. There was no facility in all South Vietnam to take care of them, nor were there any trained specialists to look after the children. It was not at all unusual to find in the overcrowded hospitals patients lying on the floors and children lying crosswise in cribs, as many as three, four, and possibly five in a bed.

After completing our survey, which was extensive, we submitted our report to the Vietnamese Ministry of Health and to the United States Agency for International Development. This report, which served as a blueprint, was accepted by both parties and we were asked to implement it. We recommended the immediate construction of a surgical hospital for the treatment of the children and, in addition, a reception and convalescent unit. The entire center was also intended for the teaching and training of Vietnamese surgeons, anesthetists, pediatricians, nurses, ancillary personnel, etc. Eventually the Vietnamese staff was to take over the operation of the center and continue the treatment, teaching, and training program.

The construction of a hospital even in a developed country is a complicated difficult task. To build and staff a hospital in an underdeveloped country during a war is immeasurably more difficult. How well the project succeeded is now a matter of record.

There were 54 surgical beds, three operating rooms, recovery room, x-ray department, pharmacy, storage, supply rooms, and a maintenance department. We also built a reception area and a 125 bed convalescent section. The center (Fig. 4) was the largest facility of its kind anywhere in the world. In 1969 the dedication of the Center was marked by the award of the Medal of Health by the South Vietnamese Minister of Health (Fig. 5). We started with a Western staff of 38 but the Vietnamese staff had been trained, and by the time we left in 1975, we had phased our all the Westerners except four.

It was not a one-man job and it could not have been accomplished without a talented and devoted staff. To mention a few, Lester Silver, M.D., Chief of Professional Staff—his commitment whole-hearted, his efforts untiring. Elizabeth Ferrer, R.N., hospital administrator and later Executive Director—she truly served above and beyond the call of duty. Joyce Horn, R.N., Chief Nurse, later Hospital Administrator—she never lost her "cool," a tower of strength and commitment. Without such dedicated people (and many more) it could never have been accomplished. Before we left in 1975 we had raised the funds and completed the plans for a burn center. During all these sad and weary war years with its neverending procession, destruction, death, and injured children, the project became for those of us engaged in it an island of hope in a sea of despair.

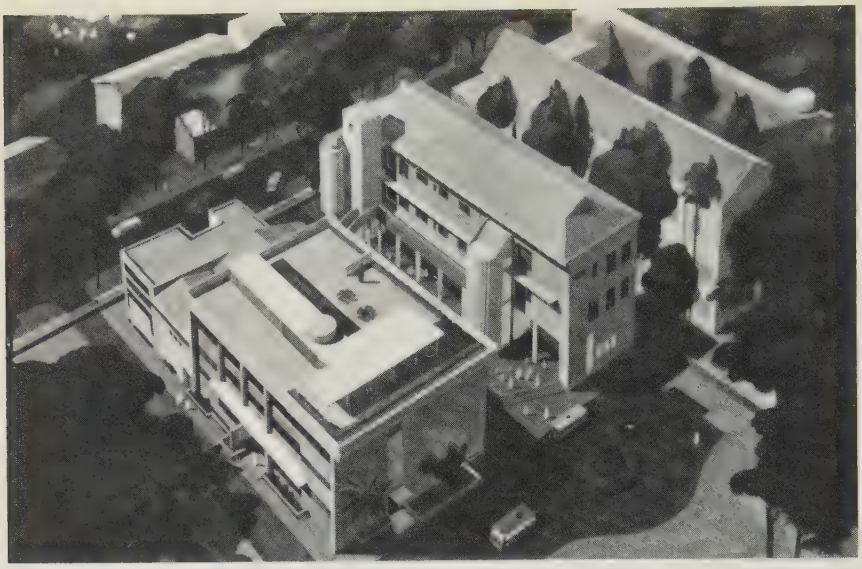
CƠ-QUAN Y-TẾ QUỐC-TẾ PHỤNG-SỰ NHI-ĐỒNG
CHILDREN'S MEDICAL RELIEF INTERNATIONAL, INC.
TRUNG TÂM GIẢI-PHẪU BỔ-HÌNH VÀ TÁI-TẠO
CENTER FOR PLASTIC & RECONSTRUCTIVE SURGERY
SAIGON, VIETNAM

Figure 4. An architect's rendering of the Center for Plastic and Reconstructive Surgery, Saigon, Vietnam. The third building in the rear was a nursing school and not a part of the Center.

In the spring of 1975, the hospital was full and we had a waiting list of over 400. I could see the handwriting on the wall—the collapse of Saigon was imminent. We had at no time participated in any politics whatsoever, confining ourselves strictly to the matter at hand, taking care of war-injured children and teaching and training the Vietnamese.

I might interject at this point that when we first arrived in Saigon in 1967, I had a conference with the then Foreign Minister (whose name escapes me), and I told him that we proposed to admit to the hospital any child that we could care for without regard to race, creed, color, or political affiliation. His immediate reply was, "No problem." And from the very beginning we were given a completely free hand in admitting patients, and I am certain that there were many Vietcong children among them. This made no difference to us. We were there to treat the children, and that we did!

With the imminent collapse of Saigon, our surgeons and the Vietnamese staff became extremely apprehensive. They were convinced that if they remained in Saigon they would be killed. It was at that time that I cabled and wrote to the representatives of the Provisional Liberation Government in Hanoi, in Paris, and in Geneva. I offered to continue to supply professional support and supplies to take care of the children. I asked in return only that the staff be given safe conduct to carry on their work. No one ever bothered to reply to the cables or the letters—none of which were returned.

After the fall of Saigon, I returned home to New York, discouraged, ill, and ended up in the hospital. When I recovered sufficiently, I flew to Paris after having made an appointment with the Provisional Liberation Government representative. I explained to him about our work in Saigon and impressed upon him the necessity of carrying on the work. He was courteous but said that he could make no decision;

Figure 5. Being awarded the Medal of Health by the South Vietnamese Minister of Health at the dedication ceremony of the Center for Plastic and Reconstructive Surgery, 1969.

the decision would have to be made in Saigon, and he asked us to submit in writing our proposition telling what we had done and what we proposed to do. I cabled New York, and within three days the papers were in his hands. I never heard any further word. Nobody even bothered to acknowledge receipt of the papers. I cannot help remarking that this complete disregard is most disheartening. We had, at the time of the collapse of Saigon, a full hospital of children—about 200 children.

It is now about two years since the fall of Saigon and we have been unable to learn the fate of our unit. We left these two well equipped, well furnished buildings; what if anything they are used for now, I have no idea, but I do know that if they were put to the use that they were originally intended for, the children of Vietnam—and I say ALL THE CHILDREN OF VIETNAM, North and South—would benefit greatly. We are still prepared to return and to carry on the work so desperately needed, but no one in Vietnam seems to care.

EPILOGUE

It is now (August 1977, 28 months since we have had to give up the center in Saigon. The fate of the children still haunts us, those whose treatment we were unable to complete, and those countless thousands who will go throughout life deformed or disfigured. We at Children's Medical Relief look back on the past with a certain sadness for not being able to carry on our work in Vietnam, but consoled by the thought that we were able to help thousands of children.

In the last two years we have carried out surveys in the Far East, Africa, and the Caribbean area. We have been indelibly impressed by the enormous need for children's reconstructive surgery throughout the developing world. We are hoping to be able to set up international centers in several of the most needy areas. Today's children are tomorrow's world, and if this sad and weary world is to be made into a better one for our children and our children's children, each one of us, whether he or she be lowly and humble or talented and great, must aid in lighting the candle to cast its glow of help and hope.

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Intensive Therapy—A Modern Necessity

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and Rita McConn, Ph.D.†

It has been our happy privilege to have been involved in the early pioneering of some of the scientific-medical aspects of intensive therapy in Great Britain. This is rather a different perspective in that it relates not the memoirs of an individual, but rather the philosophy arising from our experience as members of a multidisciplinary team in intensive care which came together in a county hospital in Lancashire in the early sixties under Dr. Eric Sherwood Jones.

Historical Background of Organized Intensive Therapy

The idea of the intensive care unit as it is found today probably had several routes: (1) major surgery has been developing rapidly since asepsis removed one of the chief obstacles to its success and anesthesia made it possible; (2) IPPV via a tracheostomy was found to provide the best means of survival in bulbar poliomyelitis; (3) the practical implications of Claude Bernard's statement that health was governed by maintenance of a normal milieu intérieur came fully home with the development of an understanding of acid-base and electrolyte changes in the body, (4) the importance of close monitoring in myocardial infarction became manifest.

Special postoperative wards and recovery rooms have long been a feature of the surgical scene, and were designed to provide a concentration of nursing personnel in close liaison with the surgeons and anesthetists concerned with the particular intervention the patient had endured. It was hoped that this would enable a closer and more enlightened supervision of the patient than would be available in a conventional "Nightingale" type ward and serve as an early warning system if deterioration in the patient's condition occurred. This was essential and the results made the extra cost of the system worthwhile because: (1) deterioration was often due to causes that developed rapidly, needed emergency treatment and were remediable (e.g., airway obstruction, cardiac arrest and hemorrhage); (2) close monitoring, e.g., of level of consciousness, urine output, blood pressure, cardiac rate and rhythm, could often prevent such disasters; (3) an ordinary doctor's social conscience would not permit him to undertake technically successful major surgery that subsequently ended in failure because of postoperative mishaps; and (4) during the polio epidemic in Los Angeles, Denmark, and Sweden between 1948 and 1953, it was found that the large majority of patients treated with cabinet respirators died, whereas a significant percentage of those treated by tracheostomy, tracheobronchial drainage, and IPPV (mostly by endotracheal intubation and manual IPPV) survived bronchoscopy, tracheostomy, and removal of tracheobronchial secretions without IPPV had been tried (Sjoberg) and found incomplete therapy. The scientific climate (from Guedel 1934 to Engstrom 1951) was ripe for the institution of prolonged IPPV via a tracheostomy with the maintenance of a clear airway.

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At about this stage in the story it was becoming apparent, e.g., in the postoperative ward, that the surgeon was not able to deal with the complications resulting from anesthesia as well as the individual who administered the anesthetic and the physician in charge of epidemiological wards was unable to cope with the demands of airway maintenance and IPPV as well as the anesthetist to whom these were routine procedures. The natural outcome of this series of events was to take anesthetists out of the operating theaters and their role of glorified technicians and bring them into contact with patients, practical therapeutics, and clinical responsibility, for which many still feel they are unqualified. In 1965 H. C. A. Lassen, who is rightly regarded as one of the pioneers in the field of intensive therapy, and who was perhaps one of the first physicians to call an anesthetist in consultation to aid in the treatment of polio, was moved to say, "The more desperately ill a patient, the more needed is a top flight specialist in internal medicine, that is, one who can use his hands at three o'clock in the morning."[6] He does not, however, go on to say what the physician should use his hands on, or how, and it is intriguing to reconstruct the view of the consultant anesthetist originally called in by Henry Lassen for help. Thus, Bjorn Ibsen has stated quite unequivocally that the person who should be in charge of such a unit should be the man who knows what to do with his hands at three o'clock in the morning. Quite obviously both are right, and if neither adopted the position of an autonomous consultant, but agreed to collaborate from a medical division, the controversy would not arise, the patient would benefit enormously, and the primary function of the doctor, which is to treat patients, would be fulfilled in the best way possible.

Intensive Care Unit at Whiston Hospital

The damp cold English winters always caused a blossoming of a fair number of chronic bronchitics into chest infections severe enough to require hospitalization. This occurred to such an extent that one whole block of the hospital, three floors each of thirty or so beds, was usually filled with such patients under the care of a chest physician, Dr. Eric Sherwood-Jones. There can be little doubt that seeing some of these patients ultimately succumb with acute pulmonary failure influenced him in opening a 4-bed respiratory unit in a so-called "side-ward" adjacent to a children's ward. He was aided and abetted in this by an anesthetist, Dr. John S. Robinson, who had recently completed his M.D. thesis on "Observations on the Effects of Passive Hyperventilation in Human Subjects" in the Department of Anesthesia at the nearby University of Liverpool. Not a surprising choice of topic, since it was in this department that Professor Cecil Gray had developed the anesthetic technique utilizing curare, nitrous oxide, oxygen, and hyperventilation. Thus Sherwood and Robinson had the required expertise to tackle the problem of acute respiratory failure. In 1962 a case report was published from the unit in which therapeutic use of muscle relaxants was described in association with treatment of crushed chest with prolonged mechanical ventilation and deliberate hyperventilation.[5]

Perhaps the word respiratory unit is a little too grand in material terms to describe two rooms at the end of an open bed ward of this former workhouse, 1100 bed hospital. However, from a physiological point of view, it was extremely civilized. Arterial blood gases were measured as deemed necessary to monitor the patient's respiratory and metabolic state. Nutrition, even in the critically ill patient, was regarded as of prime importance, since it was always Sherwood's contention that starvation is rare in Britain outside hospitals. Those patients, unable to be fed orally received a high caloric high protein diet based on a milk product and lactose via a nasogastric tube. A metabolic balance, including fluids, electrolytes (Na^+, K^+ and Cl^-), and nitrogen, was done daily on each patient in the Clinical Research Laboratory. The fact that this was another small room, tucked away at the end of another ward, with benches built of plywood "pinched" from the hosptial store, did not negate the validity of the measurements. While the blood gas system was international, a Severinghous CO_2 electrode (U.S.A.), a Bishop oxygen electrode (England), pH capillary electrode based on that of Astrup (Denmark), the flame photometer was a Sherwood original. Original to the point of not only being hand made, but incorporating his son's perspex ruler which served as the scale for

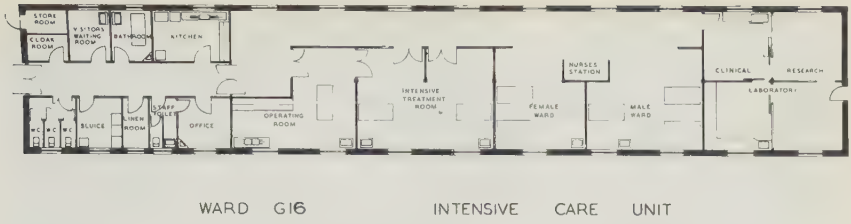

Figure 1. Floor plan of the ICU at Whiston Hospital.

the galvanometer, while the top of the flame chamber proudly bore the ground glass stopper of a candy jar. "Digital read-out" was by means of the operator constructed calibration curve, and, best of all, as an instrument it was extremely accurate and reliable.

Sherwood long recognized that the team of physician-scientist-nurse was basic to the concept of good intensive care. Furthermore, he realized that the field was an area rich for clinical investigation. Lacking the American umbrella of N.I.H., financial support for clinical research in England was hard come by, especially if one was not a major teaching hospital. However, by hook or by crook, Sherwood was able to raise the salary for a science graduate to join the team and this is how one of us (Rita McConn) joined the team. One of the first lessons to be learned by a newcomer was that "Union Rules" did not apply to the Intensive Care situation and that one wore whatever hat the situation demanded. Cleaning a room from top to bottom for admission of a new patient was frequently a team affair, blood gas electrodes "out of order" were often the item of team consults, while it even influenced the dietary habits of team members through the development of Sherwood's liquid diet. Such "volunteers" to determine the nutritional needs of a normal subject were readily identified by the large urine collection bottle that accompanied them everywhere—from ward to pub—displaying their daily urine output for all to see. It was indeed not only a scientific advance, but of comfort to the "volunteers," when the problem of lactose intolerance was solved and the addition of methyl cellulose to the diet provided the necessary bulk![8]

In 1962 the Liverpool Regional Hospital Board was sufficiently impressed to award funds for the establishment of an eight-bed intensive care unit at Whiston Hospital which served a population of 300,000. A single storey Emergency Medical Services ward built in 1940 was converted at a cost of 5,000 pounds by the hospital engineering, maintenance, medical and nursing staff. Figure 1 shows a diagram of the lay-out, whereas Figure 2 illustrates the patient care areas.

Pharmacologist and departmental chairman, Professor Andrew Wilson, had the foresight to persuade the University to designate this unit the Clinical Pharmacology and Therapeutics division of the University. Thus official academic standing opened further doors and two registrars, Dr. John Peaston, an internist, and one of us (M. Ambiavagar), an anesthetist, joined the team. The next four years saw not only the treatment of wide variety of acutely-ill patients but the development of various therapeutic advances. Part of this material formed the basis of two doctoral theses: "Metabolic Care of the Critically Ill Patient" (J. Peaston) and "Recognition of Tissue Hypoxia in Hypotensive States" (R. McConn), and an M.D. thesis on "The Therapeutic Use of IPPV" (M. Ambiavagar). Thus Sherwood realized in practical terms intensive care of the critically-ill married to clinical investigation.

Table 1 is a list of patients admitted to the unit between 1962 and 1966 placed in broad categories with a view to illustrating the nature of the clinical problems involved, the sort of service the unit provided, and the results obtained. A number were admitted for investigation with the special facilities available (11 of 14 myasthenics) and others were admitted for closer monitoring than was possible in ordinary wards. No postoperative cardiopulmonary or neurosurgical patients were treated since this surgery was performed in another regional hospital.

"The Cost of Life"

With the progress of time it became clear that not only was there a therapeutic challenge but also an ethical problem to be resolved. The therapeutic team of

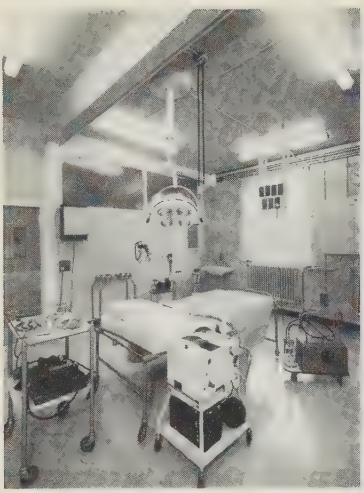

Figure 2. *Top left*, This room was equipped as an operating room used for anesthesia, bronchoscopy, tracheotomy, controlled ventilation, and dialysis. Total area—350 sq. ft. *Top right*, Two treatment rooms were separated by a folding partition. The partition was put in originally because of shortage of nurses so one nurse could monitor two patients simultaneously. However, it became apparent subsequently that infection, noise, etc. were minimized in a single room. The sliding door was kept closed. *Bottom right*, Two open wards—three beds for men and two for women, joined by a nurses' station. These beds were used for monitoring patients with an open tracheostomy or those requiring continuous monitoring who may at any moment deteriorate sufficiently to require intensive care.

nurse-doctor-scientist needs to be skilled in the application of procedures such as ventilation, nutrition, renal dialysis, etc., but in addition a very special kind of experience of the natural history of disease is required. Let us attempt to explain by means of Figure 3. With the passage of time, bodily functions in health decline slowly. In the presence of disease, say chronic bronchitis, the decline of function is more rapid and life expectancy is shorter. This much is known. Now if an acute exacerbation occurs, as at A, a rapid decline in function occurs which would have

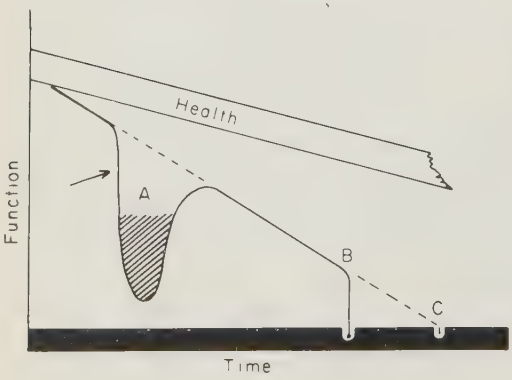

Figure 3. Reproduced from Jones, E. S.: Organization and administration of intensive patient care. Postgrad. Med. J., 43:341, 1967, with permission.

TABLE I

REASON FOR ADMISSION	NUMBER ADMITTED	DEATHS	AVERAGE DURATION OF STAY IN I.C.U.
Respiratory Disease:			
1. Chronic Bronchitis and cor pulmonale	77	19	7.5 days
2. Pulmonary embolism	1	0	15 "
3. Status asthmaticus	30	5	8 "
4. Chest injuries	25	7	7 "
5. Mendelson's syndrome	2	1	6 "
6. Other causes of respiratory failure	71	15	5 "
Cardiac Disease:			
1. Myocardial infarction	11	6	7 days
2. Cardiac arrest	7	2	3 "
3. Valvular disease	8	2	7 "
Metabolic Disorders:			
1. Metabolic care	16	1	7 days
2. Renal Disease not requiring dialysis	7	1	1 "
3. Patients requiring dialysis	12	6	17 "
Poisoning:			
1. Barbiturates and tranquillisers	52	5	5 days
2. Others	6	0	3 "
1. Polyneuritis	4	2	27 days
2. Other Neurological Cases	10	7	9 "
3. Myasthenia Gravis	14	1	7 "
4. Status epilepticus	6	1	8 "
5. Tetanus	1	0	24 "
6. Post-op. surgical cases (Plastic)	9	0	6 "
7. Miscellaneous	41	15	8 "
TOTALS	410	96	

resulted in death 20 years ago. Application of basic procedures of the ICU can now save a life, though perhaps not restore original function. There can be no doubt this intervention was justified. The patient has been given a new lease on life and, whereas the natural history of the disease up to point A was already known, the natural history from A onward is only being elucidated in recent years. To illustrate how incomplete our knowledge is in this area, let us describe the embarrassment of being faced with this patient at point B, when residual function is so poor that one has to decide whether or not to resuscitate. Current feeling is not to resuscitate, but the Danish approach is different. They resuscitate and end up with a respirator-dependent patient who needs "after-care." Being endowed with a highly developed social conscience the Danes have organized after-care in such a way that these respirator-dependent subjects are integrated back into the community, but that is another story. Whatever the pros and cons of this situation, the Danes are enriching their field of experience and this kind of knowledge is an essential component of the intensive therapist's make-up. Table 2 illustrates the experience obtained at Whiston over a 4 year period with chronic bronchitis treated by prolonged IPPV for acute respiratory failure. Of 25 patients, 9 survived 6 months to 3 years, of whom 3 were severely disabled with dyspnea. This is probably an appropriate junction to mention the cost of such a service to the community. Some describe the service as an expensive care unit and our reply to that is that it is the cheapest way of providing this kind of therapeutic service and that the real question is not "what is the cost of a life?" but rather "what is the value of a life?"

TABLE 2

Respiratory treatment of acute-on-chronic lung disease

Whiston, May 62-66

1. Age

	No. Of Patients
40-50	6
50-60	11
60-70	8

Total 25 (22 men and 3 women)

2. Duration of ventilation mean 10.6 days (range 12hrs. - 35 days)

3. Deaths during respirator treatment

Cause	No.of Patients	Day of Treatment
Failure of resuscitation	2	1
Massive pulmonary infarct	1	3
Undiagnosed carcinoma of bronchus	1	6
Perforated duodenal ulcer	1	24
Renal failure	1	11
Cross infection	2	10
Bronchopneumonia	1	13

Total 9.

4. Deaths within 1 year

Cause	No. of Patients
Progressive Corpulmonale	3
Uncontrolled bleeding due to anticoagulants.	1

Total 4.

5. Deaths within 2 years

Cause	No. of Patients
Progressive Corpulmonale	3

Total 3.

6. Follow-up of 9 patients surviving for 6 months to 3 years.

Disability	Grade of dyspnoea	No. of Patients
Moderate	1-2	6
Severe	3	3

Who Should Head the ICU Team?

The true benefits of intensive therapy are similarly intangible but nevertheless very real: (1) reduction in morbidity and mortality, (2) revised psychology of patient care, (3) laboratory for testing new ideas in nursing organization, (4) research, and (5) development of new techniques of treatment and perfection of the old.

These benefits are only realized with a medical-scientific team. In the authors' experience of this unit and other units in Great Britain, Scandinavia and the U.S., there is seldom any difficulty in determining the components of the therapeutic team required to deal with any given situation. There is, however, frequent violent and irrational controversy over who should be the head of an intensive care unit, particularly in Britain. In practice the problem has usually been solved parochially by accepting a working arrangement with an interested individual ensuring continuity of the service. The dispute arises out of trying to determine which specialty

is best suited to the job, so it is perhaps particularly appropriate that the dispute should be most evident in diploma-conscious Britain. Anesthetists claim that only anesthetists are suitable heads of ICU's on the nebulous and self-contradictory basis that they are clinically neutral and have no vested interest in beds. Similar extreme views are held by physicians who have restricted the anesthetists' function in the treatment of respiratory failure to leaving written instructions on the ventilators for the nurse to follow. Each is an example of closed-shop thinking and seeks to deny the basic fact that for years now therapeutic teams, whose components have varied to suit the circumstances, and within whom functional leadership has passed from one member to another, as was appropriate, have provided effective therapeutic service. The futility of such disputes could be mimicked in sport. For example, if those concerned with football sat down to establish in principle that a player who plays in a particular position should automatically be captain of the side. The analogy is further valid up to the point that different teams use different playing formations with overlapping expertise among the members.

The basis of the dispute, which must be a reflection of friction among members in some teams, is probably to be found in the system of autonomous consultants whose psychological self-assurance depends on control of a number of beds with complete clinical responsibility for the patients. In this circumstance "sharing" a patient with another consultant of equal status would be abhorrent. The clinical scientist or the consultant with some experience of clinical science is accustomed to trying to solve problems and rarely finding more than a partial solution. The problem is larger than the personality and he is forced into a position of humility that enables team work. This attitude is a valuable component of the psychological make-up of the modern specialist who is increasingly forced to accept help and advice from other specialists. Wade has suggested that the day of the autonomous consultant is nearing its end to be replaced by hospitals with medical or surgical divisions without individual consultant beds,[9] but the question of legal responsibility presently held by the primary care physician would have to be resolved.

In practice, however, the intensive care unit functions as such a division, it is apparent that it is desirable to appoint a suitable individual to ensure continuity of treatment, and reduce to a minimum confusion that may arise from different specialists indicating their wishes to the nursing staff at different times of the day without consulting the views of the other specialists concerned. The team concept must remain paramount and the coordinator must accept that his most important function is to streamline its working. In this it is important for him to realize that it is not solely an appointment of honor but rather a full-time responsibility which has no place for "absentee landlordism." Finally, to this point he should realize that the respect of his colleagues is not demanded but earned from his ability to function effectively and practically at three o'clock in the morning, and that he should have learned not only the language of his team members to communicate effectively, but also be conscious that he leads a democratic, not an autocratic society.

Nursing Staff

The biggest bugbear in the practical application of intensive therapy is obtaining and maintaining adequate nursing staff. This is a worldwide problem and militates against providing single room facilities. The problem has been found insoluble in several centers which accept the risk of cross infection and favor an open plan with several beds grouped around and visible from a central nursing station. Recent years have seen a partial solution through the use of single bed cubicles. In these instances two conditions must be satisfied—adequate bedside monitoring must be linked with a central monitoring installation sited at the nurses station, and a rapid safe communications system must be provided for the nurse to obtain help quickly.

It is important to recognize that despite the elegant design of a unit, electronic monitoring and on-line computers for physiological and biochemical data, the nurse is the chief therapist and her training should never be overlooked. It was the aim at Whiston to have five fully trained RN's per ventilator patient per 24 hours, but this was never achieved. The permanent staff were always overtaxed and invariably worked more than the required 44 hours, and later 42 hours, per week. Staff "borrowed" from other parts of the hospital were unhappy at having to spend a spell

in the unit and the permanent staff were seldom satisfied. The arrangement was found to be undesirable. Our experience in other centers have shown us that the nursing situation is almost universal.

At Whiston only state registered nurses were accepted for training and a four month postgraduate full-time course recognized by the Nursing College of England and Wales was instituted. The reason for excluding nurses in-training was based on practical convenience rather than established principle. It is the authors' view that all student nurses should spend 6 months in the ICU and they would derive great benefit from this. This would have been inappropriate in the early pioneering days of intensive care but nursing routines have now been standardized and a spell of nursing the severely ill and the attendant responsibility this entails cannot but stand a nurse in good stead.

There is much vague talk about the psychological "suitability" of personnel for intensive care units and the emotional strain involved. There is agreement on only one point that the ability to work harmoniously as in a team is essential. It also appears to be accepted that intensive care nursing is strenuous. There are several aspects of the "emotional strain." The patient's progress is more directly dependent on this minute-to-minute vigilance of the nurse than is usually the case in intermediate care wards and general wards. This vigilance is similar to that an anesthetist has to exercise during a complicated operation and the nurse is prone to the boredom that results from repeated monotonous observations in the same way an airline pilot is. The better the nurse's understanding of the significance of the measurement or procedures she is carrying out, the more effective the vigilance becomes. This may lessen the boredom of her task but it does not eliminate it. Finally, it is perhaps true that some psychological readjustment is necessary in accepting and using the mechanical and electronic gadgetry that is usually concomitant in intensive care, and in doggedly caring for patients who appear to be and sometimes are incurably ill. It is also necessary for the nurse to adjust to the fact that long periods of boring repetitive work alternate with periods of hectic activity and that these changes in pace are in the main quite unpredictable.

The Challenge

Most diseases have been described. It is much more difficult now than in Sydenham's time to describe a disease by observation. Epidemiology and the protection of the health of the community are now advanced sciences. The course and mechanism of disease are usually elucidated by biochemists, immunologists, and physiologists, but the problems arising from disease are first noted by the clinician. Intensive therapy is a new field as wide open as the field for Sydenham. Clinical investigation is never easy but it reaches a supreme art in intensive care. Patient care and clinical investigation must be done by the same team. Sir Thomas Lewis perhaps foresaw this when he wrote in 1933 on Clinical Science, "It is essential that those who have held charge of patients and have studied phenomenon in the living should themselves, and not through skilled deputies, explore the tissue changes which may underlie disturbed function. . . ." "Knowledge that is applied usefully to the health of mankind will almost always come by a series of steps, the first of which is the recognition of the human problem. It is therefore in the nature of things however many steps may intervene, that the first and last should be clinical. He who can see the source of the problem, who can appreciate the fittingness of its final solution, is uniquely fitted to guide the whole train of thought and inquiry."[1] The challenge of investigation in the acutely-ill is that it offers the mystique and gratification of achieving the salvage of human lives that would have otherwise been lost.

The Clinical Research Laboratory in the I.C.U.

While there has been much written in recent years on design, equipment, philosophy, etc., of intensive care units, little has ever been said directly about laboratory facilities. There are two sides to this particular aspect. One is the acquisition of laboratory data for patient monitoring, the second one arises from measurements required to answer the questions posed by the team in their quest to make therapeutic advances. The former requires standard measurements such as routine blood and urine chemistry, hematology, etc. The turn-around time from

sample collection to availability of results to the ICU staff is often critical. Thus, while automated procedures are available for these parameters, their efficiency in this particular situation is questionable in terms of comparatively small number of samples arriving at the laboratory at various times with a "stat" request attached. Ideally the unit should have its own laboratory. There can be little doubt that Sherwood's foresight in providing simple routine measurements of electrolytes, urinary nitrogen and blood gases and pH within the intensive care unit greatly facilitated therapeutic decisions. Technician problems were non-existent since team members were able to perform the necessary analyses. However, it is realized that this solution is not practical in many situations. Our experience in running a 24 hour laboratory with its own technical staff within a Surgical and Burn 12 bed ICU unit in the U.S.A. in a large municipal hospital enabled such luxuries as 4 hour metabolic balances available in badly burned adults and young children. Furthermore, the technicians were regarded as part of the team, were always aware of the patient's condition, and were therefore highly motivated. However, it was a financial burden that with increasing patient costs the institution was unable to carry, and financial cutbacks have resulted in the severe curtailing of services from the ICU laboratory with an increasing dependence on the hospital laboratory. While provision of a "stat lab" service and automated delivery of laboratory data from the central laboratories may alleviate the problem to some extent, there remains a strong case for the provision of a research laboratory within a ICU area. The type of laboratory will be an expression of the motivation of team members to answer the therapeutic problems which pose themselves.

Our experience at Whiston taught us that large sums of money or expensive equipment are not essential for many types of imaginative research. In fact, stimulated by "necessity being the mother of invention" the team built much equipment from what was available, for example, a peristaltic pump for hemodialysis was constructed from 3 nails set in a triangular formation on a piece of wood and driven by a used sewing machine motor. This Lancastrian upbringing made it hard for us to accept the "built-in obsolescence" philosophy of some transatlantic manufacturers of medical and laboratory equipment. It also endowed us with an urge to look inside those "expensive magic boxes" shown by representatives in which one simply "plugs in" the patient or sample and the "sought-after index" is displayed digitally and "at a mere X dollars more" typed out for permanent record!

With a scientific curiosity much greater than the financial resources a variety of problems were tackled in the Whiston unit, ranging from design of intravenous diets using amino acids and fat, and intragastric diets for the acutely-ill, treatment of crushed chest by IPPV, resuscitation of the moribund asthmatic, vector cardiography in chronic bronchitis, tissue O_2 measurements in normovolemic and hypovolemic hypotension, etc. In 1966 a symposium was held in Liverpool on Intensive Therapy with colleagues from Britain, Scandinavia and Europe.[1] In looking back much of the proceedings of this meeting are now routine ICU practice. Technical advances in electronic monitoring, hemodynamic measurements, ventilators and computers have had a profound impact on the direction of investigation in the critically ill in recent years. There is however nothing that can replace clinical judgment and scientific curiosity.

It is with sadness I close this chapter alone, as Dr. Ambiavagar died suddenly in April 1977. He was not only a fine human being, a compassionate and gifted physician and teacher, but he also enjoyed the therapeutic challenge of intensive care medicine, and the problems it posed. Perhaps one of the most enjoyable aspects which we both learned at Whiston was an informal exchange of ideas with colleagues. I will close with an example of this since it reflects so well the spirit behind this particular issue of the Clinics. The following is a copy of a letter written by Ambi in 1968 from Singapore to Dr. Martin Gold, Professor of Anesthesiology at the University of Maryland. Dr. Gold had written to him at Whiston asking about the technique of pressure volume loops Ambi had published[2] and on treatment of status asthmaticus.[3, 4] The original figures (Fig. 4) from the letter are reproduced.

"Dear Professor Gold:

"Thank you for your charming letter which has traced its devious path 'round the world to me. You have stimulated me to think about a research project I was forced to abandon a year ago much to my regret. On receipt of your letter I revised a

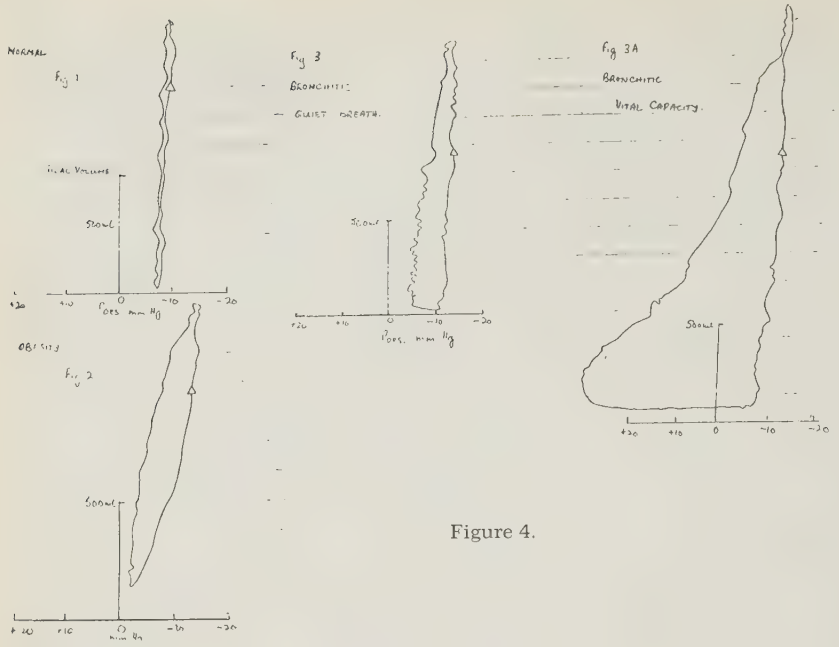

Figure 4.

great deal of unpublished data on pressure volume loops and it occurred to me you might be interested in my early thinking on the subject and some of the results it produced. If not, just drop this in the bin.

"It was apparent in those days that modern technology made available to me more biologically significant data than the computer between my ears was able to integrate, evaluate and interpret. The full significance of meticulously measured data of accepted parameters of lung function was not immediately appreciable to me in acute situations where they were most needed.

"I thought at first this must be due to the fact that the core-store, or memory of the computer between my ears was inadequate to integrate all the data necessary to help me make quick and meaningful decisions from the new input data presented to it by measurements of compliance, resistance, etc., in acute situations. I felt an on-line computer would solve my problem. It went against the grain to capitulate to a computer but this eventuality never really arose because no such computer was available. Appraising the situation afresh another possible way of resolving the difficulty presents itself. Perhaps the human computer was unable to cope because the programming was faulty—the input data was wrongly presented.

"Computers like their data numerical and presented serially, piece by piece, but human beings are different in that to us, as the words of an Old Chinese saying, a picture is worth a thousand words. It seemed possible that if simultaneous measurements of inter-related biological parameters were made and then plotted against each other on one diagram with several axes the result would be—

1. a characteristic picture for each set of measurements
2. a picture that would change with changing biological conditions giving rise to the possibility that
3. this changing picture may represent changing biological conditions accurately enough to serve as a measure of changes if
4. appropriate parameters were chosen, accurately measured, and then suitably plotted against each other.

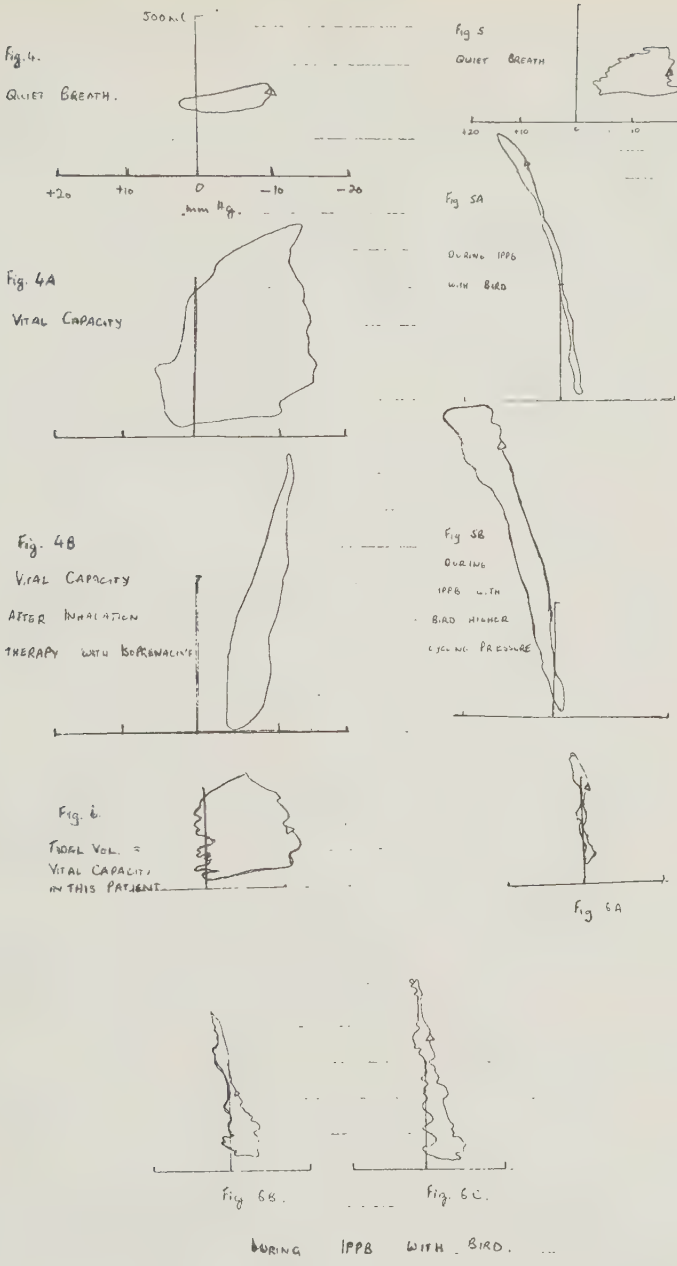

Figure 4 *Continued.*

"The pressure volume loop represents this idea in its simplest form, two parameters only, each varying continuously with the other. These are also the two measures of most direct consequence to those of us who employ intermittent positive pressure ventilation as a therapeutic procedure.

"I would like you to evaluate some results of formalizing this concept so you can decide on the validity or otherwise of my agreement that Shape-perception is one of the more evolved human faculties and that this faculty can be made to work for us in scientific medicine.

"Figure 1, like those that follow, is a tracing from the original of a respiratory pressure-volume loop showing the scales of the rectangular coordinates used. The inspiratory line is marked with an arrow. Figure 1 was obtained from a normal healthy subject breathing easily and quietly. Comparison with the next figure (Figure 2) also obtained from a "healthy" individual of the same age who was admitted to the hospital for treatment of gross obesity is revealing. Larger pressures are associated with a similar volume; the second loop is "fatter" representing a greater work out-put for the same gains, if you'll pardon my colloquialism. Attempts to record a vital capacity loop on the normal subject shown in Figure 1 were unsuccessful, because with the scales that had been chosen, the ordinate on the X-Y plotter, was too small to accomodate the loop. It was an off-scale diagram.

"Figure 3 and 3A was obtained from a chronic bronchitic with severely limited exercise tolerance who was able to earn his living at a sedentary occupation. The broadening of loop 3 signifies increased airway resistance, but the vital capacity loop is really interesting. This vital capacity is limited; the bulge towards the left at the end of respiration perhaps represents greatly increased airway resistance towards the end of forced respiration and it is obvious a very significant pressure is developed in the thorax to make complete exhalation possible. Figure 4 was from a bed-fast respiratory cripple whom the good books would describe as a "pink-puffer." This man lived at home and was subject to frequent attacks of severe breathlessness which his family doctor treated with isoprenaline inhalations and injections. The attacks usually come on at night and aminophylline was more effective.

"When Figure 4 was obtained the patient was not having an exacerbation of bronchospasm. Figure 4A shows the gross diminution of vital capacity and appears to indicate increased resistance during both inspiration and expiration. Although not in an attack of wheeze, inhalation therapy using isoprenaline from a Bird ventilator for 30 minutes, made the patient feel "easier". This pressure-volume diagram after inhalation therapy is shown at 4B. Vital capacity has increased and intrapleural pressures have decreased.

"Figure 5 was obtained from another chronic bronchitic—this time a text-book "blue-bloater", who was severely incapacitated by his illness. The picture indicates both inspiratory difficulty and expiratory spasm. This patient benefited from inhalation therapy, again with a Bird ventilator and pressure-volume loops were recoded *during* a therapy session (Fig. 5A and 5B). Figure 5A shows that larger tidal volumes result from small intrathoracic pressure changes. Such aided breathing results in effective volumes at little "cost" in terms of effort. The effects of increasing ventilation-cycling pressures on tidal volume was next investigated, and it soon became apparent that exceeding an optimal cycling pressure on the machine merely caused increasing intra-pleural pressure without increase in tidal volume—as indicated by the following of the top of the loop in 5B.

"Figure 6 is a vital capacity loop from a respirator dependent bronchitic. The next three figures are from this same patient ventilated with a Bird ventilator. The effects of varying inspiratory flow-rate, keeping cycling pressure constant, was recorded in severe obstructive airways disease. A high flow-rate was used in 6A and this was progressively reduced in 6B and 6C. Tidal volume increased with a decreasing flow-rate at a constant pressure setting.

"These measurements brought home the realization (a) that an optimal cycling pressure and an optimal flow-rate were necessary for optimal ventilation in the individual patient and (b) that pressure-volume loops aided the choice of these settings for each patient.

"I have described in previous publications (e.g., Ambiavagar and Jones 1961) that these loops helped to distinguish the drug resistant asthmatic requiring IPPV and bronchial lavage from the severe asthmatic who will eventually respond to drug therapy.

"Naturally a loop of any size or shape can be produced by varying the calibration of the axis, etc., but for a standard set of measuring settings strictly comparable loops will result. It will be apparent from the foregoing that this study is in its infancy and a great deal of work needs to be done before one can evaluate the practical usefulness of the concept. To me, after much consideration, this work seems worth undertaking. I'll even stick my neck out and suggest that if P-V loops grow up in the right way, they may end up as useful as electrocardiograms.

"Pressure-volume loops have also been displayed continuously on a display oscilloscope during IPPV as a means of monitoring ventilation. Early results showed that they were an alternative to expired gas volume measurements and machine manometer pressure measurements. They appear to provide more accurate information than these conventional measurements. Again, data is insufficient to draw conclusions.

"Since the July 1967 paper was written, many asthmatics have been treated at Whiston and the series now exceeds 50 patients. The method of treatment remains—

1. continued drug therapy, i.e., steroids, antibiotics, etc.
2. intravenous fluid infusion
3. intermittent positive pressure ventilation.
4. bronchial lavage.

"General anesthesia is used only to alleviate the distress of conscious patients subjected to intubation and bronchial lavage.

"I have always held that four of the above measures must be concurrently applied for success of the method in this type of patient and the omission of one of these is likely to lead to failure of the therapeutic effort. I am unable to prove this conclusively because I feel that a clinical trial would be unacceptable to the circumstances. I am aware that several variants of the method exist; e.g., those of Thompson and Pryor, of Ramirez and of Simpson. I disagree with these. I also think that the research schemes on this subject that many of the English and Scottish teaching hospitals have in hand will not be rewarding for the investigators. The answer to the problems posed by this method will not be found in surfactant extracts.

"Paul Herzog and Olof Norlander at the Karolinska Sjukhuset in Stockholm and Ulf Hedstrand of the Akademiska in Uppsala will be able to answer your interest in the use of subtraction circuits for compliance and resistance. John Ernsting and his team at Farnborough also have done magnificant work that will be of interest to you, but I expect you know all about this.

"With kindest personal regards, I am

Sincerely yours,
M. Ambiavagar

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Post-traumatic Metabolism: A Multidisciplinary Challenge

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My discovery of the basic phenomena which constitute what I described later as the metabolic response to injury came about in this way. I had just graduated in Medicine at Glasgow University, having taken an earlier degree in pure chemistry. During my medical course I conducted some research under the late Professor E. P. Cathcart, a pupil of C. Voit and F. G. Benedict—mainly during weekends and vacations. Before graduating I had published my first paper on the distribution of phosphorus and fat in the resting and fatigued muscle of the cat with a note on the partition of phosphorus in the blood. Just as I was about to graduate and greatly to my surprise, I was on Cathcart's recommendation appointed to the post of Lecturer in Pathological Biochemistry at Glasgow University and Clinical Biochemist to Glasgow Royal Infirmary.

These were new posts and I had to set about building up a small department where none previously existed. I was fortunate to establish a small metabolic unit comprising two three-bedded rooms and a small dietetic kitchen so that everything was controlled by the sister in charge, who was also responsible for the preparation of the meals. This was one of the earliest metabolic units in the United Kingdom. While waiting for apparatus to arrive I went round the wards of the infirmary questioning senior members of staff on lines of investigation which they would like me to tackle. One of the surgeons, George H. Stevenson, suggested I might try to find out the reason why fractures of the lower third of the femur were slow to heal. The obvious approach to this seemed to be the carrying out of calcium and phosphorus balances.

Influence of Prolonged Rest (1929)

It was soon evident that while there was usually a slight negative balance of calcium following the fracture of a major long bone, there was an excessive loss of phosphorus which, during the first period of observation, namely the second week of healing, might amount to 1 to 2 gm of phosphorus daily. As there was also an excessive loss of nitrogen, this pointed to the possibility that muscle wasting might be responsible. It then became necessary to gain an understanding of the fundamental problem of metabolism produced by prolonged immobilization.[13] Volunteers in perfect health or patients admitted to the hospital ahead of their operation of meniscectomy were confined to bed with one limb encased in a well padded osteotomy splint, the foot piece being "anchored." In some experiments the activity of the other leg was limited by being tied loosely to a sandbag. The patients were propped up in bed, and asked to limit, as far as possible, all superfluous movements.

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Within a day or two from the commencement of the period of prolonged rest there was a rise in the excretion of sulphur, nitrogen, phosphorus, and calcium.[13] The losses were maintained for a varying period, after which they gradually declined. The rise in the excretion of sulphur was due to a practically proportionate increase in inorganic sulphate, and the rise in the excretion of nitrogen was due to a limited increase in the amount of urea. Ammonia excretion also rose but more slowly. The sulphur:nitrogen ratio suggested a sulphur-rich source of the excreted materials, presumably for the most part to be muscle.

The Catabolic Response to Injury (1930)

It was established that in normally healing fractures there was a marked urinary loss of nitrogen, phosphorus, and sulphur. The rate of loss reached a maximum about the second to sixth day and then gradually declined. There was still a slight but continuous loss, even after the lapse of 1 or 2 months. Sulphur nitrogen, and phosphorus nitrogen ratios suggested that the material catabolized was probably mainly muscle. A catabolic loss of sulphur, nitrogen, and phosphorus resulting from nonbony injury was also found. In my findings published in 1930[14] I asked whether early and rapid catabolism of tissues could be associated with the first signs of regeneration of the injured part. I advanced the teleological proposition that an injured animal in consequence of the nature of its injury is faced with a diminished food supply. "The necessity is urgent and the body may require to catabolize its reserves to meet both the exigencies of repair and of maintenance." In simple disuse the catabolic disturbance, although not of the extent sometimes found associated with injury, appears to be qualitatively the same. Similarity of response, however, could not be taken as an indication that the primary causes were identical.

My general assumption at that time was that the protein reserves are being catabolized in an endeavor to maintain a constant level of metabolism, following on the earlier and more rapid exhaustion of the carbohydrate reserves, and that any slight increase in heat production is due to the specific dynamic action of the protein being catabolized. There would seem to be in addition to this temporary and early acceleration of protein catabolism, a more prolonged phase involving also probably fat in a special effort to meet an urgent need.

Urinary Nitrogen and Sulphur (1931)

Further observations suggested that an increase in endogenous catabolism following injury was not characterised by Folin's "constant catabolites," even though their origin seemed endogenous.[15] With hindsight, I now realize that protein is catabolized in greater amount following injury because of either a failure of synthesis of absorbed amino acids arising from digestion, due to an anti-anabolic phase following injury, or arises from truly endogenous catabolism of labile tissue proteins. It is still uncertain which of these metabolic processes is responsible. The bulk of the evidence indeed suggests that both anti-anabolism and excessive catabolism of endogenous protein may be operating seriatim or with overlap, and that not all protein components involved are behaving in the same way at any one time. Almost immediately after a serious injury there occurs in varying degree, but in probably all cases, the phenomenon of "wound shock." There is often also an immediate effect allied to syncope, but in some this may be delayed by the patient's unawareness of the injury, as in the intensity of battle. Later, however, the reaction sets in and is in nature providential, as it may further lessen bleeding, if present.[16] Following on this primary or initial stage of shock the area of injury generally suffers further damage through continual movement, and the patient's condition is rendered worse through further haemorrhage, exposure to cold, and anxiety. These circumstances aggravate the condition, and with varying intensity there then frequently develops a more serious type of shock in that it is more prolonged and at one time was termed "secondary wound shock." This generally persists as long as the injured person is subjected to noxious stimuli. The intensity of these phenomena varies amazingly in different individuals, even when wounds of apparently the same severity have been inflicted.

During the stage of depressed vitality of subnormality, there may be relative or absolute anuria, occasionally lasting 24 hours. With a return to more normal conditions there is still a diminished urinary volume lasting for another day or two, frequently with a temporary slight albuminuria; thereafter the output slowly rises, often irregularly, to a volume practically double the amount passed during the early days. The maximum urinary volume was generally not attained until about two days after the maximum urinary excretion of nitrogen had occurred. The earliest specimens of urine available indicated relatively normal amounts of nitrogen, sulphur, and phosphorus, but these values soon rose rapidly reaching in the case of nitrogen a value sometimes two or three times the intake. This occurred between the fourth and eighth days in accidental injuries.[16] Faecal losses were not appreciably affected.[19, 34]

It was generally found that the maximum daily loss of nitrogen was proportional to the total loss whether estimated over 5 or over 10 days. The total loss during 10 days in one case reached as high a figure as 137 gm of nitrogen, a reduction in the nitrogen content of the body of 7.7 per cent. Evidence was found that an injury such as a dislocation of an ankle might produce as great a disturbance of metabolism as the splintering of both bones of a leg. It was found that a double osteotomy on the femora of a rachitic undernourished boy, aged 16 years, produced a much less marked disturbance of metabolism than occurred in a boy of the same age who had both bones of one leg broken in a motorcycle crash.[14] This difference I attributed mainly to the adequacy of splinting and warmth applied to the first patient immediately following the operation.

The maximum excretion of urinary sulphur (mainly sulphate) coincided with, or occurred on, the day following that of nitrogen (mainly urea). In the group of postoperative cases these peak values were reached earlier, generally on the second to fourth day. The material being catabolized was relatively rich in sulphur, having a S:N ratio of 1:13 to 1:14. This value is somewhat higher than the generally accepted value for muscle (1:14 to 1:15). The reason for this may be that the material in muscle being catabolized has not an S:N ratio the same as the total tissue, or that the sulphur moiety, even over a period of 10 to 12 days, is still being catabolized more rapidly than the nitrogen moiety.

The curves of the urinary excretion of total phosphorus, like that of sulphur, held a course parallel to the urinary output of nitrogen; the peak value sometimes coincided in time with that of nitrogen but sometimes lagged two days behind. The P:N of 1:7.7[16] indicated that muscle and also, but to a smaller extent, probably bone, were the sources.[16]

The metabolic disturbance was found to be independent of the use of anaesthetics in the manipulation of injured limbs. It was appreciated that any factor which tends to set up an arthritis also leads to a wasting of the muscles of the corresponding joint. Therein probably lies the explanation of certain of the effects which follow such simple operations as meniscectomies.

Body Temperature and Oxygen Consumption (1932)

During the initial period of depressed function the patient's heat production and body temperature were diminished, but during the subsequent phase of enhanced vitality there was generally an increase in heat production and body temperature. With few exceptions did the rise in temperature exceed 2° C. Coincident generally with the rise in temperature was a rise in pulse rate, the rate of increment being 10 beats per 1° F. But in certain cases with pronounced alterations in the urinary end products, little or no change in either pulse rate or temperature was observed.

The curves of the urinary excretion of nitrogen and the basal consumption of oxygen were generally parallel to the oxygen fluctuations and, while generally coinciding in time, might precede or succeed corresponding changes in nitrogen by 24 to 48 hours. From a search of the literature I found that these observations were in general agreement with those of Malcolm (1893) who in his book on "The Physiology of Death from Traumatic Fever" noted that there may be on occasions evidence of increased nitrogen metabolism following a major operation, yet the temperature remains at a low level.[46]

Following the attainment of these maximum values, all these metabolic increments declined over several weeks; in particular body temperature and pulse rate. The oxygen consumption was not followed for a sufficiently long period to decide what its ultimate level might be. The loss of 7.7 per cent of the body's content of nitrogen was considered too great an amount to come from the local area of damaged cells alone. I considered that it must be of some more general origin than the local alone.[16]

Effect of Massage and Passive Movement (1932)

Massage supplemented by passive movement, when applied for even 20 minutes per day to patients convalescing several weeks after fracture of one or more of the major long bones, caused generally, but not constantly (seven of nine investigations) a decrease in the urinary excretion of nitrogen, sulphur, and phosphorus. Muscle and bone appeared to be the tissues chiefly affected by this anabolic activity.[17]

Effect of Injury on Plasma Proteins (1935)

It had long been known that the level of fibrinogen in the blood plasma is very variable and that acute inflammations are invariably associated with high values. Foster and Whipple (1921 to 1922) had shown that dead tissue and a nonspecific (aseptic) inflammation were the only factors necessary to cause the increase of fibrinogen in the blood,[38] and Gavaerts and de Harven (1928) had noted a rise in the fibrinogen content of the plasma following aseptic operations.[39]

Using a salt fractionation technique described by Hawk and Bergeim (1927), Tompsett and I noted that fracture of one or more of the long bones of the leg or an excision of knee joint caused an immediate and marked disturbance in the total amount and in the relative proportions of the different plasma proteins. The general effect was a slight fall in albumin coupled with a marked rise in the globulin fraction. Fibrinogen was often appreciably raised.[33]

Dietary Requirements of the Injured (1936)

The question naturally arose whether increased intake of foodstuffs, protein in particular, could stem the loss of body substance due to trauma. I found that if diets very rich in first-class protein and of high caloric value were eaten by patients who had suffered fractures of one or more long bones of the leg, the considerable loss of body nitrogen which normally occurs under such circumstances is considerably reduced. At the height of the catabolic response, however, such diets still failed to prevent loss of protein. Measures such as massage and manipulation, the addition of meat extractives, extra glycine, hydrolysates of mixed ox tissue, gelatin, and sodium caseinate, and diets of high caloric value but average protein content, similarly failed to stem the loss of protein and generally proved less successful in mitigating the drain on the body's reserve.[19, 20]

Additional to following the urinary output of N, S and P, K and Na were also studied to some extent. It was apparent that while the excretion of P and K varied with that of N, Na remained fairly constant. The fact that K rather than Na was the variable element suggested that cellular material was being catabolized. These observations were made after such shock as occurred was over. The creatinuria which developed and paralleled the rise in total N was accompanied by little or no change in creatinine excretion.[20]

I suggested that the actual fracture of bone might not itself cause much disturbance compared to the trauma arising from the tearing of the soft tissues by the traumatic agent and the bone fragments. I concluded that the overall beneficial effect of a diet of high protein and caloric content in diminishing wastage which generally results from injury is sufficient to warrant advising the provision of such diets to injured patients after the period of shock, for they modify the marked loss of body protein.

Experimental Trauma Model (1939)

In 1934 I had been persuaded to change from my location in a department of Pathological Chemistry with hospital facilities to the more academic role of Grieve

Lecturer in Physiological Chemistry but still within Glasgow University. The advantage of this was to bring me in closer contact with Professor E. P. Cathcart, an eminent authority in the field of protein metabolism, and give me much more teaching experience in practically every branch of physiology. It also provided me with the assistance of honours students of whom Dr. Hamish N. Munro, and the late Dr. Alec Isaacs of interferon fame, were probably the most notable.

I had felt that there were certain aspects of the response to major trauma which could best be answered by seeking an experimental model on which to test out our problems. With the help of a young surgeon, J. S. M. Robertson, who afterwards became the senior neurosurgeon and founder of the Neurosciences Institute in the West of Scotland, and J. L. McGirr, a young honours biochemist who was also to have a distinguished career, I studied fracture of the femur of the rat by open operation under ether anaesthesia as the standard injury. This injury caused a definite loss of nitrogen, sulphur, phosphorus, potassium, and creatine in the urine. Sodium and preformed creatinine remained relatively constant or occasionally fell slightly. These findings were comparable to those in man and were not due to the anaesthetic per se, nor could such extensive metabolic changes be produced from simple incisions of skin and separation of muscles without fractures.[28] The loss of body substance could not be fully accounted for by the loss of muscle substance from the site of the injury or from the injured limb. There appeared to be, in addition, a generalized increase in catabolism to meet the exigencies of the enhanced metabolism of the recuperative process. Additional dietary carbohydrate exercised a definite sparing effect on the general loss of tissue substance, but did not appear to prevent appreciably the local wastage. Cuthbertson and Munro (1937)[27] had already shown in normal man that additional carbohydrate not only spares tissue protein and fat where there has been an energy insufficiency, but if taken in excess, so that the total energy of the diet is greater than expenditure, may cause nitrogen retention.

Analyses of muscle from the injured and uninjured limbs indicated that the loss of potassium was relatively in excess of that of nitrogen. On the assumption that the excess nitrogen came from muscle, the loss of muscle substance could account for four fifths of the total loss of body weight. We presumed that the reserves of carbohydrate and fat were also called on to meet the demand for readily oxidisable material.[28]

Action of the Anterior Pituitary Gland (1941)

The next experiments to be described were first planned on a Glasgow railway platform, where I was seeing Professor F. G. Young (now Sir Frank Young) off to London. He suddenly said, "I wonder what would happen to your injured rats if you gave them some of my crude alkaline extract of the ox anterior pituitary." I said, "Let's try."

Given to a rat suffering from a fracture of one femur, the extract prevented the loss of body weight and excessive excretion of nitrogen and of creatine which we had already found to result from such an injury.[35] No beneficial effect was observed on the restoration of the atrophied muscles of the injured limb.[29]

Despite the capacity of this extract to promote growth in normal rats and to prevent loss of body weight and tissue nitrogen in rats with a fractured femur, it had no significant effect on the total period required to heal wounds caused by removal of circular discs of skin from the upper thighs.[30]

Action of Metabolic Stimulants (1944)

With the assistance of T. H. C. Barclay and A. Isaacs it was found that dried thyroid gland and also 2-4-α dinitrophenol when fed to rats caused a significant reduction in the mean time required for healing, the former by 12 and 22 per cent in the two experiments performed, the latter by 15 to 27 per cent. These two substances have the common property of increasing the rate of oxidation in the tissues and inducing a slight rise in general body temperature.[3]

Ebb and Flow Phases (1942)

I introduced the term "ebb" to characterize the period of depressed metabolism associated with the initial phase of the reaction to moderate to severe trauma

recognized also as the period of traumatic shock. This fitted in with existing observations in the literature. With hindsight I now realize that this could have also accounted for a general inhibition of protein synthesis following the injury, although certain acute phase reactant proteins increase.

I used the term "flow" for the phase of increase in metabolic rate in those that recover from the "ebb" phase. This is also the period sometimes termed traumatic inflammation, and is characterized by the marked rise in the urinary excretion of nitrogen, sulphur, phosphorus, potassium, and creatine, whereas there is generally no rise in sodium or creatinine; indeed these may fall slightly.[21]

Protein Hydrolysates (1944)

In 1944 I drew attention to the use by Elman and Weiner (1939)[37] of an intravenous solution of an acid hydrolysate of casein fortified with tryptophan (which is destroyed during digestion with acids) and which was also supplemented with additional methionine or cystine as the levels of these were considered inadequate.[23] I advised then that this kind of preparation "should not be used routinely unless the ability to ingest, digest or absorb protein is seriously impaired."[24]

A Summary of Research (1945)

I outlined the main causes of protein depletion after injury: (1) actual loss of tissue; (2) loss of blood or exudate from the traumatized area; (3) loss due to excessive protein catabolism and to the general reaction to infection, if present; (4) loss due to disuse or reflex atrophy. I calculated the protein losses arising from these causes for the first 10 days or so in a case with a burn involving the whole thickness of skin over 60 per cent of the surface as: (1) 700 gm; (2) 600 gm; (3) 700 to 800 gm; (4) 100 gm; some 2 kg in toto. Skin grafting would also probably lead to a further reaction and depletion.[22] By this time several other groups of investigators were contributing substantially to our knowledge.[1, 2, 5, 11, 12, 40, 41, 45, 50, 51]

In 1945 I wrote, "Practically all clinical observations go to indicate that it is doubtful whether during the early catabolic phase, any dietary measure can effectively suppress the catabolic destruction of protein."[22]

Rowett Institute Research

I was appointed Director of the Rowett Research Institute in 1945 in succession to Lord Boyd Orr, then Sir John. This meant that my primary concern was now to be furthering our knowledge of the nutrition of animals of agricultural importance and, in consequence, I could only devote a small fraction of my time for the next 20 years (till my retirement) to the metabolic consequence of injury.

In 1952 I was delighted to receive from Dr. Francis D. Moore a copy of his unique early series of surgical cases studied by metabolic balance in the Peter Bent Brigham Hospital[47] and interpreted in terms of the clinical and biochemical facts by application of his keen insight. It was entitled *The Metabolic Response to Surgery*. I was very much honoured by his very generous references to my early contributions. I was interested to learn that his negative nitrogen rates were quite in accord with the general magnitudes I had observed.

Then in 1959 appeared the papers by Levenson and Watkin[44] and in 1962 that by Kinney[43] which did much to illumine the nature of the catabolic response, the former emphasizing that their isotopic experiments provided evidence of both depressed anabolism and accelerated phases of post-injury catabolism, the latter defining the quantitative catabolic response to different types of injury. I reviewed the field in 1964[25] and at intervals since as new evidence emerged.

Heat Production Consequent to Injury (1957)

During one of these interludes my colleagues Cairnie, Campbell, Pullar, and I (1957)[6] investigated by means of a gradient-layer calorimeter they had made, the increases in total heat loss and in urinary nitrogen of rats following fracture of a femur, both on an adequate protein diet and on a practically protein-free diet. On the former the small heat increment observed over 14 days corresponded to that which could have been derivable from oxidation of the non-nitrogenous residues of amino acids corresponding to the extraurinary nitrogen excreted, both in mag-

nitude and course. There was no indication of an increase in fat oxidation. A re-examination of my earlier (1932)[16] data on accidental injuries on man revealed the same kind of parallelism early after injury. Rats maintained on the protein-free diet did not exhibit these rises, presumably because the readily metabolizable protein (amino acid) pool had already been used up, confirming the observations in 1943 of Munro and Cuthbertson.[49]

Further observations indicated that a single oral dose of β-methasone, a powerful anti-inflammatory drug, produced in the rat an increment in urinary nitrogen comparable to fracture of femur, but strangely there was no corresponding heat increment. However, reducing substances were found in the urine indicating incomplete oxidation. Fracture plus drug induced the summated effects of these agents.[10]

Effect of Environmental Temperature on the Response to Injury (1966, 1967, 1968, 1972, 1973)

When I retired as Director of the Rowett Research Institute, former students of mine now on the staff of Glasgow Royal Infirmary invited me to return to continue my researches within the department which I had started in 1926. I was fortunate to secure a research grant from the Medical Research Council for this purpose.

This line of work which I had begun at the Rowett Institute I now transferred to Glasgow Royal Infirmary where after 13 years of official retirement I still am working, albeit now only two days a week. My Medical Research Council Grant ceased after some five years.

I had suggested in 1932 that the increase in oxidative metabolism with increased heat output as the result of fracture of a long bone both in man and the rat might be due, in part, to a reaction to speed up the rate of healing by raising body temperature. It was therefore interesting to find that Caldwell (1962)[7] had found in the rat that at an environmental temperature of 30° C this normal metabolic response to burning injury in his experiments did not occur when the animal's intake of food was fixed at the pre-burn level, whereas animals with similar wounds but maintained at 20° C, also with their diets fixed at the pre-burn level, lost weight, had a high mortality, and exhibited a negative nitrogen balance. When both environmental groups were allowed free access to food in the post-burn period these striking differences between the groups were not seen and the adverse effect of restriction at the lower temperature disappeared. The rate of wound healing was found by Caldwell to be significantly faster at an ambient of 30° C than at 20° C, with both groups having free access to food: the mortality was then low in both groups and not statistically different.

Campbell and I also found that in rats, maintained both before and after fracture of a femur within the zone of thermoneutrality for the rat (30° to 32°C), no catabolic response occurred either in the shape of increased heat production or increased urinary nitrogen output.[8, 9] Moyer (1962)[48] showed that the excessive oxygen consumption in burned rats could be prevented by covering the burned areas with an impermeable material.

On ad libitum feeding Caldwell found the response to fracture in the rat was generally much less marked, even apparently absent at 20° C, but interpretation was complicated by a fall in intake after injury on ad libitum feeding.[7] The explanation offered by Caldwell to account for the disappearance at 30° C of the normal increased heat production following burning was the reduction of the charge on the animal's heat production mechanism to evaporate the water exuded from the burned surface. We argued that fracture of bone as induced by us did not expose a wet surface such as is seen in burns, and yet a comparable reduction was seen within the zone of thermoneutrality.

Following this experiment I visited Professor S-O. Liljedahl's research group, then in Stockholm, and was impressed by the good state of severely burned patients being nursed in a relatively dry atmosphere with warm air (around 35° C) blowing over their exposed bodies (Barr et al., 1968;[4] Davies and Liljedahl, 1970[36]). With my colleagues G. S. Fell, Catherine M. Smith, and W. J. Tilstone,[26] and Rahimi,[32] we showed in man that the protein metabolic response to moderate to severe injury involving fractures of one or more major long bones is also reduced by placing the patient soon after injury in an environmental temperature of 28 to 30° C, and a

relative humidity of 35 to 45 per cent.[26, 31, 32] In general, the patients tolerate the warm drier conditions. The advantage of the higher environmental temperature over extra bed coverings is mainly related to the reduction of total resting heat production to the basal values provided by the thermoneutral conditions. Injured extremities are kept warmer. The disturbance of the plasma proteins is also reduced. Experimentally wounds heal faster at the higher temperature.

EPILOGUE

To one who commenced work on the metabolic response to injury some 50 years ago, the recent fresh outburst of research activity in this most rewarding field for multidisciplinary study is most encouraging. This is in large part due to the realization and appreciation of the significance of the reactions which John Hunter described two centuries ago as inducing "both the disposition and the means of cure,"[42] and also in part is due to the evolution of techniques for intensive care including intravenous nutrition.

We realize that our knowledge of the integrated neuroendocrine response to trauma has not advanced as it should. The integration and timing of these activating influences, such as the autonomic outflow and the homeostatic readjustments, are now much better understood but there is still a great deal but dimly comprehended. The translation of these into the mobilization of body stores is, as I have already stated, still imperfectly understood.

With each fresh discovery there is revealed an ever deeper facet of the cellular response to injury which provides the various disciplines interested in the physiological and metabolic response to injury with a great and continuous stimulus and resolve "to understand both the means and disposition for cure."

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Parenteral Nutrition

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The Amino Acid Period

Parenteral nutrition is a recent development in human medicine. When I started my medical training in 1938, no one was using this method. The only procedure which had any connection with parenteral nutrition was the intravenous application of a 5 per cent glucose solution and a physiological saline solution. During the second year of my medical training at Karolinska Institute Medical School in Stockholm, Sweden, I had the great privilege of serving as assistant to Dr. Erik Jorpes at the Department of Chemistry. Dr. Jorpes was, at that time, deeply engaged in his now so classical studies of heparin, a substance which had been isolated by him a few years earlier. Among other things, he developed a method, by which heparin could be prepared on a large scale for intravenous use. In cooperation with Dr. Clarence Crafoord, he also investigated the possibility of using heparin for the prevention and treatment of thromboses of various types. Dr. Jorpes, with his broad interest in nutritional problems, especially those related to protein, gave me the impetus to make amino acid analyses of protein.

In those days, no chromatographic methods were available for study. This meant that many of the individual amino acids had to be isolated before determination. At that time, it seemed logical that I should simultaneously investigate the possibilities to produce an amino acid mixture that could be used intravenously in conditions where a patient could not be fed orally. Given an intravenous supply of amino acids, it should be possible for the patient to maintain or replete the stores of body proteins. Both Dr. Jorpes and Dr. Crafoord convinced me that there was a large number of patients with severe and even fatal complications caused by protein malnutrition, which may have resulted of underlying disease or operations. This area of research seemed very fascinating to me. Dr. William C. Rose at the University of Illinois had a few years earlier made investigations resulting in the discovery of threonine as the last of the essential amino acids. These studies furthered my interest in that same field and from time to time I was encouraged by Dr. Jorpes and Dr. Crafoord to clinically apply this knowledge of essential amino acids. It seemed to me logical and even plausible to provide intravenous protein nutrition with amino acids. It was also suggested that it might be possible to make a complete parenteral nutrition schedule as an alternative to oral feeding. I am sure that all of us at that time thought that complete parenteral nutrition should be included in the area of science fiction. However, I could not let go of this fascinating idea and decided that I should start exploring the field of amino acid mixtures for intravenous nutrition.

At that time, it was impossible to obtain crystalline amino acids at a reasonable cost. I felt that two alternative routes of investigation could be followed. One was the use of an amino acid mixture obtained by hydrolysis of a protein with high biological value. The other possibility was the use of synthetic amino acids. From many points of view it seemed reasonable for me to start with an enzymatic hydrolysate of casein. My decision was influenced to a large extent by reading a

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paper by Henriques and Andersen published in 1913.[21] In that paper, a positive nitrogen balance was reported in a goat given an enzymatic hydrolysate of meat protein by the intravenous route. However, I chose casein because it was fairly easy to produce in pure form. The main problem was isolating the amino acids from the crude enzymatic casein hydrolysate and eliminating all remaining proteins and enzymes as well as high-molecular peptides, which might produce allergic or other adverse reactions.

Dialysis seemed to be the answer. With this method all high-molecular peptides and substances producing allergic reactions were separated from the low-molecular peptides and amino acids, which were able to readily penetrate the dialysing membrane. By using the resulting dialysate, it was possible to obtain an enzymatic casein hydrolysate containing only amino acids and some low-molecular peptides. However, there was still the problem of making this dialysis aseptically on a large scale. This was finally solved by the simple but important method of performing the dialysis at an increased temperature at which no bacteria or other microorganisms could grow.

In order to procure infusion solutions to be used in man, it was necessary to have them produced by a pharmaceutical firm. This was the reason why I started my cooperation with the Vitrum Company, which at that time was owned by the Bjurling family. Two brothers, Bertil and Gösta Bjurling, were actively engaged in the firm. They decided to support my investigations and efforts to develop solutions for intravenous nutrition. Gösta Bjurling, who was a pharmacist, and I had very stimulating discussions concerning all problems in this field. Soon a properly prepared infusion solution containing a dialysed, enzymatic casein hydrolysate was available for use in man. The clinical studies were performed in close cooperation with my colleagues at the Department of Surgery at Sabbatsberg's Hospital in Stockholm. Dr. Clarence Crafoord was at this time Head of the department. However, most of these studies were carried out 25 years ago in cooperation with Dr. Fritz Lidström. We showed that the enzymatic casein hydrolysate, which was given the trade name Aminosol-Vitrum, could significantly reduce the protein loss in the postoperative patient. Thus, the negative nitrogen balance in the postoperative period was much less conspicuous than with the administration of an equivalent volume of glucose solution. This observation has recently been confirmed by Blackburn et al.,[2] who suggested that amino acids should be used postoperatively instead of glucose alone to counterbalance unnecessary losses of body proteins. We also observed that it seemed easier to reduce the negative nitrogen balance in severely malnourished patients than in well nourished patients. Similar findings have been reported by several authors, among them Bozzetti et al.[4]

During our initial work, we were spurred in our efforts by reading reports published a few years before in this field on protein hydrolysate by Dr. Robert Elman (1937) of St. Louis, Mo.[12] During the following decade, from 1940 to 1950, there were numerous reports from various parts of the United States and Europe on the intravenous use of enzymatic protein hydrolysates to cover the requirement of protein.

The protein hydrolysates were shown to be well utilized as amino acid sources for parenteral nutrition. But, the peptides in the preparations of protein hydrolysates were only partly utilized. Another disadvantage was that the amino acid pattern depended on the protein being used for hydrolysis and not on the pattern which the nutritionists would like to have. Consequently, we felt it was of great importance to develop preparations containing pure crystalline amino acids in optimal proportions. A lot of hard work was carried out in my laboratory to synthesize the individual amino acids.[35] It was demonstrated that rats could grow on diets containing the synthetic essential amino acids as the sole nitrogen source. However, it was noted that the racemic synthetic amino acids were not utilized to the same degree as the natural L-forms. Isolation of the L-form from the racemic DL-amino acids was found to be very difficult and impractical. These problems were studied during my stay with Dr. W. C. Rose at the University of Illinois for a year as visiting Professor. My work to obtain amino acids synthetically was eventually discontinued, due to easy commercial access of pure crystalline L-amino acids from Japan. This simplified the process of producing amino acid mixtures with an optimal composition.

A large number of preparations containing crystalline amino acids soon appeared on the market. Some of these formulations had incorrect amino acid ratios and produced nutritional imbalance. In some cases, a large amount of the inexpensive amino acid glycine was used for the sole purpose of giving a high nitrogen content. However, the nutritional value was low and there was also the risk of ammonemia. Experimental as well as clinical studies proved that the best utilization of an amino acid preparation was obtained when the aminogram corresponded to that of proteins with high biological value. This meant that all essential and nonessential amino acids found in these proteins should be included in intravenous amino acid solutions as an alternative to protein for oral or enteral feeding.

There has always been a great deal of discussion and speculation about the possibility of using amino acid mixtures with special properties for various conditions. Bearing this in mind, it was certainly most fascinating when special amino acid preparations were found to be useful in uremia and liver coma. Giordano[15] found that urea-nitrogen in the body could partly be used to synthesize nonessential amino acids. When a mixture of essential amino acids was given to a uremic patient, part of the urea-nitrogen could be used for the synthesis of the nonessential amino acids, which are necessary to form body protein with the essential amino acids supplied. In this way, a decrease of the urea-nitrogen can occur. This hypothesis has repeatedly been confirmed by other investigators.

In liver disease with coma, a disturbed pattern of the free amino acids in the blood has been noted.[13] The most important changes are decreased levels of the branched-chain amino acids and increased levels of the aromatic amino acids and methionine. This results in an abnormally large accumulation of serotonin formed from tryptophan in the brain. Also, the high level of phenylalanine causes formation of the abnormal octopamine in the brain and a disturbed catecholamine metabolism. The low level of branched-chain amino acids increases the uptake of tryptophan in the brain. When an amino acid solution is administered which normalizes the amino acid pattern in the blood, the comatose patient suddenly awakens. The effective amino acid preparation contains a high amount of isoleucine, leucine and valine, as well as low concentrations of phenylalanine, tryptophan, tyrosine and methionine. The effect observed on the patients with liver coma will probably depend on the pharmacological action of the amino acids, and not on their nutritional value.

Energy and Amino Acid Utilization

It was soon observed that, in most cases, a positive nitrogen balance could not be obtained with amino acid preparations alone. Various studies indicated that the supply of nonprotein energy was of great importance in reducing the negative nitrogen balance and increasing the utilization of the amino acids supplied. At that time only glucose solutions were available as sources of nonprotein energy. The concentration of the glucose in these solutions could not be higher than 10 to 15 per cent due to the risk of thrombophlebitis in the peripheral veins. In those days all infusions had to be made peripherally. We tried the addition of ethanol to glucose in order to increase the nonprotein energy.

In a study with my coworker of several years, Dr. Oscar Schuberth, the utilization of Aminosol-Vitrum was increased from 56 to 96 per cent by the simultaneous infusion of ethanol in an amount corresponding to 1060 kcal or 150 g per day. This amount of ethanol is very close to the maximum amount (about 175 g) to be oxidized in man per day. In spite of the favorable effect of ethanol on amino acid utilization, we came to the conclusion that ethanol was not a suitable nonprotein energy source for parenteral nutrition, because of its pharmacological and toxicological effects. It was obvious that the nonprotein energy for intravenous nutrition had to be covered in some other way. Two different methods were developed: the lipid-carbohydrate system with fat emulsions given in a peripheral or central vein and the glucose system supplied in a central vein only. When safe fat emulsions became available,[30] the lipid-carbohydrate system was introduced in Stockholm, Sweden. This lipid system consists of fat emulsion and glucose or fructose as nonprotein energy sources. The glucose system (hyperalimentation) with glucose as the only nonprotein energy source was developed by Drs. S. Dudrick, D. Wilmore, H. Vars and J. Rhoads (1968) in Philadelphia.

Fat Emulsions for Intravenous Nutrition

During all our discussions concerning an ideal nonprotein energy source, we turned to fat mainly because of its high energy content. Although the results of previous studies with various types of fat emulsions for intravenous nutrition were not very encouraging or stimulating, I could not accept the statements made by several investigators that it was impossible to prepare a suitable fat emulsion for intravenous nutrition. Natural chyle from the thoracic duct was certainly proof that the body itself could produce a suitable fat emulsion to be tolerated when supplied intravenously. My aim then was to prove that such a fat emulsion could also be produced in a laboratory or factory. I received financial and moral support from Mr. Gösta Bjurling at Vitrum. Also, my friend and coworker, Dr. Oscar Schuberth, aroused my enthusiasm for further efforts and investigations by promising to perform the clinical tests if and when I could get a fat emulsion which was proven nontoxic in animal studies.

I and my assistant, Dr. Ivàn Håkansson, prepared a large series of fat emulsions containing every conceivable type of suitable fat and emulsifier. I personally visited a large number of investigators, who had previously tried to prepare fat emulsions for intravenous use. Among these investigators, Dr. Pieter Sorgdrager of Utrecht, Holland, working with an olive oil emulsion attracted my special attention. I also stayed a few months with Dr. Robert Geyer and Dr. Fred Stare at the Department of Nutrition, Harvard University, School of Public Health in Boston. Dr. Geyer and his associates gave me most valuable information about their studies on a cottonseed oil emulsion corresponding to Lipomul. However, all these visits did not aid in my efforts to produce a non-toxic fat emulsion. At that time, I realized that no further progress in the development of an intravenous fat emulsion without adverse effects could be made in the absence of an adequate animal test system. In such a system, the amount of fat given should correspond to a substantial part of the total energy requirement for this particular species of animal. It was considered reasonable to supply about 100 per cent of the basal energy requirement. The main reason for this decision was that in a starved animal nearly all energy expenditure is derived from fat and only to a minor extent from body protein. When the test animals were dogs, daily doses of fat amounting to 9 g/kg body weight should therefore be used. Since the basic energy requirement in man is roughly ⅓ of that of the dog, 9 g fat/kg in dog would correspond to 3 g fat/kg in man. The test system in dog seemed to be a reasonable foundation for proving the tolerance of a fat emulsion suitable to cover the nonprotein energy in man. The period of daily infusions should also last a sufficiently long time; 28 days was considered adequate.

For a long time it seemed impossible to find any fat emulsion which could be given to the test animal without causing severe adverse reactions with fatal outcome. The results from these early investigations indicated that the highest tolerance was obtained by using oils and phospholipids as native as possible. The most promising fat was soybean oil and the best emulsifying agent was eggyolk phospholipids. My hypothesis was that the adverse reactions we observed could be avoided by proper preparations of the oil and phospholipids. After a large number of trials and errors, I finally developed a method to produce suitably prepared soybean oil and eggyolk phospholipids. A fat emulsion produced from these raw materials showed no toxic or other adverse effects when tested in animals. The dogs survived and remained in good condition throughout the planned test period of 28 days with daily infusions of the fat emulsions in an amount of 9 g of fat/kg body weight.

This new fat emulsion with the trademark Intralipid (Vitrum) was in fact the only fat emulsion tested by us and found acceptable using our newly devised animal test system.[17] All other commercially available fat emulsions tested at the same time resulted in severe adverse reactions and fatalities during the test period.[22] The reason for this varying toxicity is, so far, unknown. There are great biological differences between the various commercially available fat emulsions, meaning that it is not correct to speak of fat emulsions for intravenous nutrition in general terms. The name of the product and its exact composition must always be stated.

Schuberth and I found that the patients tolerated Intralipid very well and certainly much better than other fat emulsions.[30] Subsequently a large number of clinical investigations in connection with parenteral nutrition were performed in

Table I. Tentatively recommended daily allowances of water, energy, amino acids, carbohydrates, fat, and minerals for patients on complete intravenous nutrition. The basal allowances will cover resting metabolism, some physical activity and specific dynamic action, but no increased needs because of trauma, burns, etc. The moderate amounts should be used when the patient has increased losses or is in a depleted status. The high supply should be used in severe catabolic conditions as burns, after trauma, etc.

	Allowances per kg body weight to adult			Allowances per kg body weight for neonates and infants		
	Basal amounts	Moderate amounts	High supply	Basal amounts	Moderate amounts	High supply
Water	30 ml	50 ml	75-100 ml	100 ml	125 ml	125-150 ml
Energy	30 kcal = 0.13 MJ	35-40 kcal = = 0.15-0.17 MJ	50-60 kcal = = 0.21-0.25 MJ	90-120 kcal = = 0.38-0.50 MJ	125 kcal = 0.52 MJ	125-150 kcal = = 0.52-0.63 MJ
Amino acid nitrogen	90 mg (0.7 g amino acids)	0.2-0.3 g N (1.5-2 g amino acids)	0.4-0.5 g N (3-3.5 g amino acids)	0.3 g (2.5 g amino acids)	0.45 g (3.5 g amino acids)	0.5 g (4.0 g amino acids)
Glucose	2 g	5 g	7 g	12-18 g	18-25 g	25-30 g
Fat	2 g	3 g	3-4 g	4 g	4-6 g	6 g
Sodium	1-1.4 mmol	2-3 mmol	3-4 mmol	1-2.5 mmol	3-4 mmol	4-5 mmol
Potassium	0.7-0.9 "	2 "	3-4 "	2 "	2-3 "	4-5 "
Calcium	0.11 "	0.15 "	0.2 "	0.5 "	1 "	1.5-2 "
Magnesium	0.04 "	0.15-0.20 "	0.3-0.4 "	0.15 "	0.15-0.5 "	1 "
Iron	0.25-1.0 /umol	1.0 /umol	1.0 /umol	2 /umol		3-4 /umol
Manganese	0.1 "	0.3 "	0.6 "	0.3 "	0.7 /umol	1 "
Zinc	0.7 "	0.7-1.5 "	1.5-3 "	0.6 "	1 "	1.5 "
Copper	0.07 "	0.3-0.4 "	0.4-1 "	0.3 "		
Chromium	0.015 "			0.01 "		
Selenium	0.006 "			0.04 "		
Molybdenum	0.003 "					
Chlorine	1.3-1.9 mmol	2-3 mmol	3-4 mmol	2-4 mmol		4-6 mmol
Phosphorus	0.15 "	0.4 "	0.6-1.0 "	0.4-0.8 "	1.3-1.5 mmol	2.5-3 "
Fluorine	0.7 /umol	0.7-1.5 /umol		3 /umol		
Iodine	0.015 "			0.04 "		0.1 /umol

Sweden as well as in the other Scandinavian countries using Intralipid. Many of these studies were carried out by my coworkers, Dr. Oscar Schuberth, and Dr. Dag Hallberg. Dr. Hallberg showed—much to my surprise—that the fat particles of Intralipid were eliminated from the bloodstream in the same way and at the same rate as natural chylomicrons. It was also demonstrated that postheparin-lipoprotein lipase hydrolysed the fat of Intralipid at the same rate as the fat of the chylomicrons. It was soon confirmed that Intralipid made it possible to provide parenteral nutrition with an adequate amount of nonprotein energy also. It was shown in 1965 that an adult patient suffering from Crohn's disease could be kept in good nutritional status for 5 months with intravenous feeding with amino acids, glucose, fat, electrolytes, and vitamins.[20] The infusions were given in a peripheral vein.

Complete Parenteral Nutrition According to the Intralipid System

When we had obtained a fat emulsion that could successfully be used to cover the total energy need, I returned to my earlier studies relating to the original idea of complete parenteral nutrition as an alternative to adequate oral food. In other words, all nutrients normally absorbed from the intestine should be able to be given intravenously. Careful reading of all available papers on nutrient requirements resulted in tentative recommendations for nutrient supply to patients on complete parenteral nutrition. It is often difficult to calculate the required amount of some nutrients to be given intravenously based on oral nutrition studies because of differences reported by various investigators on absorption from the intestine. More studies are certainly needed before we have an exact knowledge of the nutrient requirements of patients on intravenous feeding.

The recommendations for nutrient intake[35] resulted in the preparation of solutions containing electrolytes and trace elements to be added to the infusion solutions for parenteral nutrition. The recommendations have been revised and the most recent version is published in cooperation with Dr. Alan Shenkin.[29] Tables 1 and 2 show these recommendations. Three levels of tentative recommendations are suggested. The supply of basal amounts is expected to prevent any nutrient-deficiency symptoms in a noncatabolic patient. The moderate and high supply should be used in situations when nutrient deficiency has been observed or is expected.

It is important to insure that no iatrogenic nutrient deficiencies occur when the parenteral nutrition is used to prevent or treat hospital starvation in patients unable to take food orally or enterally. To prevent deficiencies, standard formulas have been worked out containing the basal amounts of nutrients, including all electrolytes, trace elements and vitamins to be used. The Intralipid system which is used widely by us in Sweden is presented in Tables 3 and 5 for adults and infants, respectively. The three main infusion solutions we use are an amino acid solution with carbohydrate (Vamin), a fat emulsion (Intralipid) and a glucose solution. All other nutrients are added in special solutions mentioned in Tables 3 and 5. In this way it is a simple matter to supply the basal daily requirements of energy and all other nutrients (Tables 4 and 6). Our goal is, of course, prevention of deficiencies in patients on total parenteral nutrition.

My colleague Dr. Stefan Jacobson kept a female patient entirely on complete parenteral nutrition, including fat, for more than seven months (1968/1969). This was the first long-term parenteral nutrition attempted in Sweden, proving that Intralipid in combination with carbohydrates was a suitable nonprotein energy source in parenteral nutrition. In this case, the infusions were made through a central venous catheter. The patient was very carefully examined and tests were made to establish energy, nitrogen, and electrolyte balances.[1] The results were those expected to be found in a patient having a good nutritional status.

There are many records of patients subjected to long-term parenteral nutrition including fat emulsion. One of the most fascinating cases of long-term parenteral nutrition has been reported by Jeejeebhoy et al.[23] The patient is a housewife (born in 1934) who has been exclusively nourished intravenously since October 1970. For the first 9 months she received treatment and instructions in the hospital. Since then, she has remained in her home and taken care of the intrave-

Table 2. Tentatively recommended daily amounts of vitamins in basal metabolic state and in conditions of increased need. The recommendations for basal, moderate and high supply are explained in the text to Table 1.

	Allowances per kg body weight per day to adult			Allowances per kg body weight per day to neonates and infants		
	Basal amounts	Moderate amounts	High supply	Basal amounts	Moderate amounts	High supply
Thiamin	0.02 mg	0.04 mg	0.3 mg	0.05 mg	0.1 mg	2 mg
Riboflavin	0.03 "	0.06 "	0.3 "	0.1 "	0.2 "	0.4 "
Nicotinamide	0.2 "	0.4 "	2 "	1 "	2 "	4 "
Pyridoxine	0.03 "	0.06 "	0.4 "	0.1 "	0.2 "	0.6 "
Folic acid	3 /ug	6 /ug	6-9 /ug	20 /ug	40 /ug	50 /ug
Cyanocobalamin	0.03 "	0.06 "	0.06 "	0.2 "	0.4 "	5 "
Pantothenic acid	0.2 mg	0.4 mg	0.4 mg	1 mg	2 mg	
Biotin	5 /ug	10 /ug	10 /ug	30 /ug	60 /ug	
Ascorbic acid	0.5 mg	2 mg	25 mg	3 mg	6 mg	20 mg
Retinol	10 /ug (33 IU)	10 /ug (33 IU)	20 /ug (67 IU)	0.1 mg (333 IU)	0.1 mg (333 IU)	0.15 mg (500 IU)
Ergocalciferol or cholecalciferol	0.04 /ug (2 IU)	0.04 /ug (2 IU)	0.1 /ug (4 IU)	2.5 /ug (100 IU)	2.5 /ug (100 IU)	2.5 /ug (100 IU)
Phytylmenaquinone	2 /ug	2 /ug	2 /ug	50 /ug	50 /ug	150 /ug
Tocopherol	0.5 IU	0.75 IU	1 IU	1 IU	1-1.5 IU	1.5 IU

Table 3. Infusion solutions with additions for adults on intravenous nutrition. The given amounts are intended to cover a basal requirement. When greater amounts are demanded 1.5 to 2 times the cited volumes should be given.

SOLUTION 1		
(a)	Solution of crystalline amino acids (7%) and carbohydrates (10%) ("Vamin with glucose")*)	1000 ml
	with the addition of a	
(b)	Solution of electrolytes ("Addamel")*) containing 5 mmol of Ca, 1.5 mmol of Mg, 50 µmol of Fe, 20 µmol of Zn, 40 µmol of Mn, 5 µmol of Cu, 50 µmol of F, 1 µmol of I and 13.3 mmol of Cl	10 ml
SOLUTION 2		
(a)	Fat emulsion (Intralipid 10%)**)	1000 ml
	with the addition of an	
(b)	Emulsion of fat soluble vitamins ("Vitalipid for Adult")*) containing 0.75 mg of retinol, 3 µg of cholecalciferol and 0.15 mg of vitamin K_1	10 ml
SOLUTION 3		
(a)	Glucose solution 20% for intravenous nutrition	500 ml
	with the addition of a	
(b)	Solution of lyophilyzed water soluble vitamins ("Soluvit")*) containing 1.2 mg of thiamine, 1.8 mg of riboflavin, 10 mg of nicotinamide, 2 mg of pyridoxine, 0.2 mg of folic acid, 2 µg of cyanocobalamin, 10 mg of pantothenic acid, 0.3 mg of biotin and 30 mg of ascorbic acid, and	20 ml
(c)	Potassium phosphate solution containing 30 mmol of K, 6 mmol of P and 21 mmol of acetate	15 ml

*) Vitrum, Stockholm, Sweden

**) Intralipid 10% may be used in an amount of 1000 ml and with 500 ml of glucose solution 20%, if no increase of the total water volume is desired.

nous nutrition by herself. The infusions, which are made during the night through a catheter of silicon rubber inserted in the vena cava superior, consist of an amino acid mixture, glucose, fat (500 ml of Intralipid 10 per cent), electrolytes, and vitamins. Studies of liver biopsy specimens revealed normal structure when fat was included in the intravenous diet.

There are many ways of proving a special feeding system to be adequate. The best way is to show that normal growth in infants may be sustained. Recent literature provides conclusive evidence that the lipid system is adequate for growing infants. The fat emulsion used will also supply an adequate amount of essential fatty acids. Børresen and his coworkers supplied complete intravenous nutrition, including fat, through peripheral vein infusion in neonates and infants.[3] In spite of severe operations for various congenital malformations, the infant grew very well and survived. Many similar observations have been reported.[7, 16]

The successful nutrition of infants by the intravenous route has convinced nutritionists that this kind of feeding is an adequate alternative to oral or enteral feeding. This is the final proof of the success of complete parenteral nutrition; it is no longer a science fiction.

Table 4. Amounts of nutrients to adults on intravenous nutrition with the solutions given in Table 3.

Energy and nutrients	Amount per day			
	Solution 1 in Table 3 1010 ml	Solution 2 in Table 3 1010 ml	Solution 3 in Table 3 535 ml	Total
Water	0.94 l	0.88 l	0.48 l	2.3 l
Energy	650 kcal	1100 kcal	375 kcal	2125 kcal
Amino acids	70 g	-	-	70 g
Glucose or Fructose	100 g	25 g[1]	100 g	225 g
Fat	-	112 g[2]	-	112 g
Sodium	50 mmol	-	-	50 mmol
Potassium	20 "	-	30 mmol	50 "
Calcium	7.5 "	-	-	7.5 "
Magnesium	3.0 "	-	-	3.0 "
Iron	50 /umol	-	-	50 /umol
Zinc	20 "	-	-	20 "
Manganese	40 "	-	-	40 "
Copper	5 "	-	-	5 "
Chloride	68.3 mmol	-	-	68.3 mmol
Phosphorus	-	15 mmol	6 mmol	21 "
Fluoride	50 /umol	-	-	50 /umol
Iodide	1 "	-	-	1 "
Thiamine	-	-	1.2 mg	1.2 mg
Riboflavin	-	-	1.8 "	1.8 "
Nicotinamide	-	-	10 "	10 "
Vitamin B_6	-	-	2 "	2 "
Folic acid	-	-	0.2 "	0.2 "
Vitamin B_{12}	-	-	2 /ug	2 /ug
Pantothenic acid	-	-	10 mg	10 mg
Biotin	-	-	0.3 "	0.3 "
Ascorbic acid	-	-	30 "	30 "
Vitamin A	-	0.75 mg	-	0.75 mg
Vitamin D	-	3 /ug	-	3 /ug
Vitamin K_1	-	0.15 mg	-	0.15 mg
Tocopherol	-	100 "	-	100 "

1) Glycerol
2) 6 g of phosphatides

The Glucose System for Parenteral Nutrition or Hyperalimentation

At the same time as the lipid system was developed in Stockholm, a second system for parenteral nutrition with glucose covering the nonprotein energy requirement was developed and thoroughly investigated in Philadelphia by Dr. J. Rhoads, Dr. S. Dudrick, and coworkers. It was interesting to learn that the general attitude toward this nutritional therapy in Philadelphia was very much the same as in Stockholm. However, we solved the problems in different ways. Both systems supply amino acids, electrolytes, and vitamins but differ with regard to the source of nonprotein energy. Our thoughts in Stockholm were from the beginning linked with fat as one important physiological energy source to be used with a basal amount of carbohydrate. The aim was also to find an infusion solution which could be given in a peripheral vein. Dr. Rhoads and Dr. Dudrick were ingenious in developing another

Table 5. Infusion solutions with additions for infants on intravenous nutrition

	Per kg per day
SOLUTION 1	
(a) Solution of crystalline amino acids (7%) and carbohydrates (10%) ("Vamin with glucose")*)	30 ml
with the addition of a	
(b) Solution of electrolytes ("Ped-el")*) containing 0.6 mmol of Ca, 0.1 mmol of Mg, 2 µmol of Fe, 0.6 µmol of Zn, 1 µmol of Mn, 0.3 µmol of Cu, 0.3 mmol of P, 3 µmol of F, 0.04 µmol of I and 1.26 mmol of Cl	4 ml
SOLUTION 2	
(a) Fat emulsion (Intralipid 10%)*)	40 ml
with the addition of an	
(b) Emulsion of fat soluble vitamins ("Vitalipid")*) containing 0.1 mg of retinol, 2.5 µg of cholecalciferol and 0.05 mg of vitamin K_1	1 ml
SOLUTION 3	
(a) Glucose solution 15% for intravenous nutrition	60 ml
with the addition of a	
(b) Solution of lyophilyzed water soluble vitamins ("Soluvit")*) containing 0.12 mg of thiamine, 0.18 mg of riboflavin, 1 mg of nicotinamide, 0.2 mg of pyridoxine, 0.02 mg of folic acid, 0.2 µg of cyanocobalamin, 1 mg of pantothenic acid, 0.03 mg of biotin and 3 mg of ascorbic acid	0.5 ml
and	
(c) Sodium phosphate-Potassium phosphate solution containing 0.1 mmol of Na, 1.4 mmol of K, 0.2 mmol of Ca, 1.61 mmol of Cl, 0.16 mmol of P and 0.5 mmol of lactate	1.4 ml

*) Vitrum, Stockholm, Sweden

method for supplying highly concentrated glucose solutions intravenously. The technique which they introduced so successfully in parenteral nutrition was the infusion through a central venous catheter. In this way it was possible to supply glucose in high amounts corresponding to the energy required. I was quite thrilled when I learned about this technique from Dr. Dudrick and his coworkers. I have never looked upon the lipid-carbohydrate and glucose systems as competing systems. It is obvious that both systems can be used to keep a patient in good nutritional condition and prevent hospital starvation and associated complications. During long-term parenteral nutrition, fat emulsion must be used in order to prevent essential fatty acid deficiency.

A number of direct comparisons of the relative nitrogen sparing effect of intravenous fat and carbohydrate have also been performed. It can be concluded from these studies that, provided nitrogen intake is adequate, then the nitrogen balance is influenced by changes in energy supply whether these changes are derived from glucose, or fat plus glucose. In the short-term at least, glucose spares more nitrogen than fat does, but the overall differences between a glucose system and a lipid

Table 6. Amounts of nutrients to infants on intravenous nutrition with solutions given in Table 5.

Energy and nutrients	Amount per day			
	Solution 1 34 ml/kg	Solution 2 41 ml/kg	Solution 3 62 ml/kg	Total amount per kg
Water	32 ml	36 ml	55 ml	123 ml
Energy	20 kcal	44 kcal	34 kcal	98 kcal
Amino acids	2.1 g	-	-	2.1 g
Glucose, Fructose or Glycerol	3 g	1 g	9 g	13 g
Fat	-	4.5 g	-	4.5 g
Sodium	1.5 mmol	-	0.1 mmol	1.6 mmol
Potassium	0.6 "	-	1.4 "	2 "
Calcium	0.68 "	-	0.2 "	0.88 "
Magnesium	0.145 "	-	-	0.15 "
Iron	2 µmol	-	-	2 µmol
Zinc	0.6 "	-	-	0.6 "
Manganese	1 "	-	-	1 "
Copper	0.3 "	-	-	0.3 "
Chloride	2.91 mmol	-	1.61 mmol	4.52 mmol
Phosphorus	0.3 "	0.6 mmol	0.16 "	0.79 "
Fluoride	3 µmol	-	-	3 µmol
Iodide	0.04 "	-	-	0.04 "
Thiamine	-	-	0.12 mg	0.12 mg
Riboflavin	-	-	0.18 "	0.18 "
Nicotinamide	-	-	1 "	1 "
Pyridoxine	-	-	0.2 "	0.2 "
Folic acid	-	-	0.02 "	0.02 "
Cyanocobalamin	-	-	0.2 µg	0.2 µg
Pantothenic acid	-	-	1 mg	1 mg
Biotin	-	-	0.03 "	0.03 "
Ascorbic acid	-	-	3 "	3 "
Vitamin A	-	0.1 mg	-	0.1 mg
Vitamin D	-	2.5 µg	-	2.5 µg
Vitamin K_1	-	0.05 mg	-	0.05 mg
Tocopherol	-	4 "	-	4 "

system are small in most cases. Important differences in nitrogen balance may only be observed in that small proportion of cases which remain very hypercatabolic for prolonged periods, when high intakes of glucose, particularly with added insulin may be very effective.

Infusion Techniques

The infusion techniques for parenteral nutrition have been carefully investigated. The oldest and simplest method is to perform the infusion in a peripheral vein. But it has its limitations because the infusion solutions must be either isotonic or have a low osmotic pressure. Otherwise, thrombophlebitis might easily occur. This means that only the lipid-carbohydrate system is suggested for parenteral nutrition in peripheral veins. The advantage of the peripheral vein infusion is its simple application in any hospital and the possibility of immediate use. From this point of view, it differs very much from the central vein infusion technique. The insertion of a central vein catheter must be made in the operating room by an

expert. The central vein catheter may be used for both the glucose and the lipid systems. It is especially useful when the patient has to be put on parenteral nutrition for a long period of time. During the infusion in a peripheral vein, local thrombophlebitis might cause interruption of the intravenous supply. A central vein catheter obviates such problems of interrupted infusions. However, the risk of septicemia with a central vein catheter is obvious. Also, many other serious complications have been reported.

All studies and reports regarding the technique for intravenous nutrition might be summarized in the following recommendations. For short-term parenteral nutrition or for an immediate need of a parenteral nutrition in adult patients, the method of choice seems to be infusion in a peripheral vein by using the lipid system. The cannula inserted in a peripheral vein should preferably not be left there more than 10 to 12 hours. The next infusion should start with a new cannula at a new place, new infusion sets, and new infusion bottles. In this way, the risk for infection and thrombophlebitis will be reduced substantially. When it is a matter of long-term infusion, the insertion of a central vein catheter will permit either the lipid-carbohydrate or the glucose system of parenteral nutrition to be used. With reference to many investigators, infusions in a peripheral vein (scalp vein or vein on the dorsum of the hand) should also be used when possible in infants and children.[7]

During the first years of long-term parenteral nutrition, the infusions were in general performed in the daytime and the nutrients were administered at about the same periods as regular food intake. Later it became customary to maintain the infusions for 24 hours a day, simply because it was easier to prevent thrombophlebitis by having an infusion running continuously instead of stopping it for some hours. Some doctors believed that the nutrients would be better utilized by the body, when the supply was slow and continuous during all 24 hours of the day. There were however no scientific investigations to support this hypothesis. On the contrary, Maini and his coworkers have in fact recently published results of studies indicating that a so-called cyclic alimentation during 12 hours daily has some advantages compared with a continuous 24 hour daily infusion period.[27] With this cyclic alimentation, a better nitrogen utilization was reported. It also prevented dysfunctions of the liver. Generally speaking, a cyclic parenteral nutrition will maintain the normal, physiological, daily cyclic metabolic pattern of the body.

Indications for Parenteral Nutrition

By definition, parenteral nutrition should be used in all conditions where the patient cannot get an adequate supply of nutrients orally or enterally. Most of these conditions are listed in Table 7. With the intravenous nutrition therapy, a good nutritional status may be maintained or obtained, which will result in improved effects of other therapeutic measures. Thus, malnourished patients might be fed parenterally *before operations* to improve their general fitness. In many *post-operative conditions,* there is often an indication for complete parenteral nutrition for a shorter or longer period of time. It is generally agreed that for the first few days following elective operations, most patients do not require any nutritional support other than fluids, electrolytes, and glucose. However, if a return to normal oral feeding is not established within 4 to 5 days, complete intravenous nutrition should be commenced. In patients who are already *malnourished prior to operation,* or when surgical complications may be expected, parenteral nutrition should be started within 24 hours of the operation.

Good nutrition is now a generally accepted prerequisite for wound healing. This also applies to *fistulas.* There are many reports of beneficial results of intravenous nutrition in patients with fistulas of various types. The closing of fistulas will then often occur spontaneously following adequate nutrition alone without any surgical intervention. This is a very good example of the body's own ability to heal, provided the supply of nutrients is adequate. Thus, another favorable effect of intravenous balanced nutrition is that the mortality rate of patients with gastrointestinal fistulas has been reported to decrease from 39 to 45 per cent to 6 to 9 per cent. This will occur regardless of whether a lipid or a glucose system is used.[8]

Intravenous nutritional support has proved successful in reducing complications as well as lowering the mortality rate in injuries such as *burns.* Many of the

Table 7. Conditions when it might be indication for parenteral nutrition

1. Preoperative conditions
2. Postoperative conditions
3. Posttraumatic conditions. Burns
4. Malabsorption or when the gastrointestinal tract needs to rest
   - Short bowel syndrome
   - Severe enteritis
   - Peritonitis
   - Ileus
   - Pancreatitis
   - Ulcerous colitis
   - Crohn's disease
   - Gastrointestinal carcinoma
5. Fistulas
6. Unconsciousness when tube feeding is contraindicated
7. Other conditions with inadequate enteral feeding
   - Chronic diarrhea
   - Chronic vomiting
   - Anorexia
   - Cachexia
   - During radiation and treatment with cytostatic drugs
8. Premature infants
9. Kidney and liver insufficiency

serious metabolic consequences of extensive burns are attributed to the increased energy requirement, part of which depends on water evaporation from the burned surface. The evaporation of 1 kg of water requires 580 kcal. The oral intake of food in these patients is often limited for various reasons. In order to supply an adequate amount of energy, protein and other nutrients, the lipid system as well as the glucose system have been used for supplementary feeding. In Sweden, Dr. S.-O. Liljedahl and his coworkers used complete intravenous feeding, including fat (Intralipid), to make sure that patients with burns were kept in a good nutritional condition. In a series of patients with burns, it was clearly demonstrated that it was possible to prevent the loss of body weight, which earlier always was the case.[26] The decrease in the mortality rate of these patients was parallel to the increased use of intravenous feeding.[25] These investigations certainly proved that good nutrition is essential for wound healing and uneventful recovery.

All early discussions concerning parenteral nutrition were related to the possibility of providing an adequate alternative nutrition to oral or enteral feeding. The enteral route was somehow always supposed to be the preferred method. However, from time to time, it was suggested that it might be of therapeutic value in some instances, e.g., severe *gastrointestinal diseases*, to exclude the oral food intake for some time and maintain the patient on parenteral nutrition. This therapy of putting the gastrointestinal tract to complete rest was soon found to be very useful in conditions such as *ulcerative colitis* and *Crohn's disease*.[11, 14] Within about 2 months of parenteral nutrition, the symptoms of these diseases usually disappear. In some instances, patients have had no symptoms for a full year after such a parenteral nutrition therapy.

Toward the end of the 1950's and during the early 1960's, Dr. Kjell Jordal from Copenhagen lectured on parenteral nutrition in patients with *cancer*. With this nutrition therapy, the patients could be reestablished in a good nutritional condition.[24] During the discussions following his lectures, many colleagues frankly stated that feeding a cancer patient resulted only in feeding the tumor and could not possibly do the patient any good and was not ethically justified. Somewhat later, Professor Cl. Solassol and Dr. H. Joyeux of Montpellier demonstrated that it certainly was very useful to maintain cancer patients on parenteral nutrition.[31, 32] They stated that this was an efficient way to put the cancer patients back into good nutritional status facilitating treatment with more extensive surgery, radiation and large dosages of cytostatics. This would not have been possible in malnourished and cachectic cancer patients. Souchon et al.[33] and Copeland et al.[6] have confirmed that parenteral nutrition in cancer patients results in greater possibilities for using specific methods of tumor treatment.

Home Parenteral Nutrition

Parenteral nutrition is in general performed on hospital patients. However, in some situations, patients on long-term parenteral nutrition have been treated in their homes. In this way it has been possible for the patients to go about their normal daily business. *Home parenteral nutrition* has been reported on by several authors.[5, 28] The indications for home long-term parenteral nutrition may be the no-bowel syndrome, short bowel syndrome, enterocutaneous fistulas, and malabsorptions due to severe intestinal diseases. It is justified in special situations and obviously requires strict patient selection, education, and training as well as interested medical personnel to assist the patient. The successful outcome of this very special kind of nutrition rests largely with the patient. As mentioned above, Jeejeebhoy et al.[23] describe a patient who has received total parenteral nutrition since 1970. Twenty patients between 2¼ and 77 years of age have been started on home parenteral nutrition by Byrne et al.[5] The reported duration ranged from 34 to 881 days. Similar reports on home parenteral nutrition have been made by Prorok et al.[28] All these studies certainly show that an intravenous nutrition may be as adequate as ordinary oral feeding. In fact, I and all scientists in this field, have been hoping and waiting for this kind of evidence.

Trends in Parenteral Nutrition

The present situation in the field of parenteral nutrition includes two systems—the lipid and the glucose system—by which a complete parenteral nutrition can be given to any patient who for various reasons cannot take food orally or enterally. The infusion techniques are very well developed and adequate when performed in the correct way. All the necessary infusion solutions and injections with electrolytes, trace elements, and vitamins are currently available. However, it is obvious that much more information about this fairly new therapy is necessary before all patients requiring it will be properly treated. It means that it will take some time to eliminate hospital starvation in the patient who cannot, will not, or must not eat. This special type of hospital starvation and its complications are nowadays mostly a matter of ignorance about simple nutritional facts. In many cases the proper name for this condition should be iatrogenic malnutrition.

However, there are still many problems in parenteral nutrition to be solved or elucidated. More balance studies on energy and nitrogen in various conditions are required. It is important to develop amino acid preparations with optimal interrelations between the individual amino acids to be used in various conditions, such as severe catabolism, uremia, and liver diseases. More knowledge about the requirements of electrolytes and trace elements in the various situations is also necessary. The different systems for parenteral nutrition can certainly be further improved toward a simpler and more convenient system.

Summary

Parenteral nutrition therapy was born 35 to 40 years ago when the first steps were taken to perform a protein nutrition by the intravenous supply of amino acids in man. Since that time, many efforts have been made to supply adequate amounts of energy intravenously. These efforts have resulted in the two available systems for parenteral nutrition: *the lipid-carbohydrate system* and *the glucose system*. The lipid-carbohydrate system, which corresponds to the nutrient content of normal food, may be given either in a peripheral vein or through a central vein catheter. The glucose system is administered through a central venous catheter.

Many problems concerning the parenteral nutrition need to be solved and further elucidated. However, our present knowledge and technique in this field are far advanced over earlier methods. Now all patients who cannot take food in adequate amounts orally or enterally may be kept in good nutritional status by parenteral nutrition. In this way it is possible to prevent starvation and its complications in these patients.

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Cinderella of Surgery—Fractures?

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It is perhaps somewhat strange that a general surgeon should find himself writing on the treatment of fractures. If you think that "specialists" who have contributed to progress in surgery are people who know more and more about less and less, I would ask you to think again. Could it not be that those who concentrate their efforts on a narrow field and contribute to its progress are mostly people of broad background, keen perspectives, and well-aware of the basic principles of surgery? Very often however, only a multi-disciplinary group-effort of open-minded people overcomes individual shortcomings. I am pleased to relate one such group venture which has now lasted two decades and may be said to have had a certain impact on trauma surgery in general and fracture treatment in particular.

In 1956, I found myself chief of surgery at Chur, the capital of a resort area in the Swiss Alps. Inevitably, the patient population included a marked number of fractures from two sources: ski-slopes and road accidents. Surprisingly, the public at large tends to look at fractures as an incidence with quite a nuisance, but without major problems.

Twenty years ago, at least in Switzerland, the surgical profession had no reason to be proud of its success in treatment of fractures, yet Switzerland could not be regarded as below average in surgical standards. Our national accident insurance had to pay compensations for partial disablement to approximately one third of the patients with tibial fractures, two thirds of those with femur fractures, and to practically all those with fractures of the weight bearing joints.

Very rarely was there inadequate bone healing at fault. Permanent damage in the majority of cases resulted from "fracture disease" induced by post-traumatic pain, long-lasting immobility and therefore lack of physiological stimulus to the locomotor system in the absence of weight-bearing and movement. These factors together lead to impeded blood and lymph circulation. This in turn induces osteoporosis as well as fibrosis in the intermuscular spaces and in the joints with consecutive adhesions leading to permanent reduction in the range of movements. Once adhesions have set in, the changes are rarely completely reversible.

Where cure is difficult, prevention becomes all the more important. It is easy to conceive that there is only one good means of prevention: physiological challenge of the injured musculoskeletal unit, or in simple terms, early, pain-free mobilisation! Is this possible? At that time, fracture treatment advised by major centers such as Boston's Massachusetts General Hospital consisted of immobilisation and avoidance of weight-bearing. On page 48 of Edwin F. Caves' famous book, *Fractures and Other Injuries*,[9] the following advice concerns duration of external fixation: tibia and fibula in older children and adults 12 to 20 weeks, femur (older children and adults) 12 to 24 weeks. This, with or without initial traction, was also the accepted treatment in central Europe, internal fixation being used only sporadically.

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Historical Background

In 1866 Billroth, the father of abdominal surgery, stated: "I can say from experience, that even the best visceral operation never gave me as much satisfaction as the successful treatment of a difficult compound fracture!"[7]

With sepsis becoming less of a hazard toward the end of the nineteenth century, surgeons strived to apply the general surgical principles of restoring normal anatomy to the treatment of fractures, using various kinds of internal fixation. Sir Arbuthnot Lane[5] and Haye-Groves[14] from England anticipated many of our modern means such as plate and nails for internal fixation. It remained, however, for the Lambotte brothers, especially Alain Lambotte,[17] to establish a most important basic method of internal fixation—screws and plates—thus neutralizing the fracture focus and restoring normal function to the injured limb quickly (Alain Lambotte was a gifted mechanic, not only on bone! Even today, there are about 40 master-violins built by Lambotte to testify to his "three-dimensional" craftmanship.) This was the fertile ground on which Robert Danis[11] could build. If Alain Lambotte was an instinctive "biomechanic," Danis had enough of an analytical mind to formulate two basic principles which were sound physically and right biologically. He recognized *first*, that stable fixation of bone fragments depends on compression forces, and he understood *second*, that bone tolerates compression to a high degree and even takes advantage of stability provided by compression to unite. The practical corollary was to introduce interfragmentary compression by lag screws and axial compression along the axes of the bone by compression plates as one important possibility of a biomechanically sound internal fixation (see Fig. 4). Using this technique he observed a hitherto unknown healing property of cortical bone—that without radiologically visible callus, which he called "soudure autogène," best translated by "primary bone healing."

Danis was also aware that paradoxically bone healing is not the main issue in fracture treatment![11] He pointed out that internal fixation was only worth its price in risk and effort when it can overcome the main disadvantage of conservative fracture treatment, that is, long-lasting immobilisation and loss of physiological stress to the bone, muscles, and joints. His lag screw as well as his compression plate gained some popularity, but not widespread acceptance. He was considered by his contemporaries to be an isolated artist whose results were hardly reproducible by anybody else.

Eggers[13] was likewise convinced of the beneficial effect of compressive forces on bone healing. He wanted the weight-bearing to help in the stabilisation of broken bones. He introduced the slotted plate which, by functional compression, was intended to give stability and bone healing. If his system fails in some instances, it is mainly due to insufficient stability. His plate is not able to neutralize all variations of torsional, sheering, and bending forces.

Internal fixation of the femoral neck fracture by Smith Petersen[41] has been one of the most important demonstrations that internal fixation should not be looked upon as only a solution to a local problem, but rather a means of preventing local as well as general sequelae of the injury by early restoration of normal function. Until then, this fracture treated conservatively not only resulted very often in delayed healing or nonunion, but in fact very often heralded death on account of a long bed rest which can be fatal.

Internal fixation of long bones by lag screws and compression plates allows early active mobilisation, but only with limited weight-bearing. Küntscher[16] in 1940 added his medullary nail. This is an intramedullary splintage of the broken bone as an alternative to the compression fixation. In short, oblique, and transverse fractures, it allows relatively early full weight-bearing and is a true "panacea" for many nonunions of the weight-bearing bones, provided they are not in too much malignment. First his method demanded a nail that would fit the medullary cavity. Later, he introduced reaming of the medullary canal. This extended the usefulness of his method beyond the middle third of the long bones. By adapting the bone to the nail, he was able to increase the area of tight contact between bone and nail, thus increasing the stability considerably.

Lorentz Böhler's[8] monumental work in accident surgery was mainly motivated by the socioeconomic aspects of the ever increasing epidemic of trauma, striking

people at their most productive age. He got extremely frustrated to see how little importance the university centers attributed to the treatment of trauma in general and to fractures in particular. Böhler, with his aggressive and creative mind, was not admitted to the inner sanctum of university surgery in Vienna. He succeeded, however, to convince the national insurance company of Austria that the high invalidity rate resulting from fractures could be considerably reduced if adequate methods would be applied. Once allowed to concentrate accident patients in special hospital units, it did not take him long to prove his point. Böhler, in fact, led conservative fracture treatment from masterly neglect to careful reduction and relatively early motor rehabilitation. To prove his point he introduced a hitherto unknown comprehensive follow-up system which allowed him to document his very didactic textbooks which were soon to become world famous. Although basically conservative, Böhler, in his long professional life, has some 20,000 internal fixations to his credit, which are to be weighted against some 200,000 conservatively treated fractures in the hospitals under his supervision. In his basically conservative attitude he had as his "Anglo Saxon" counterparts, Sir Reginald Watson-Jones[8] in England and Edwin F. Cave[9] in Boston. Thus, some 20 years ago, internal fixation of fractures as an alternative to long-lasting external fixation, while probably sound in principle, had largely fallen into disrepute for three reasons:

1. Most of Böhler's and Cave's surgical contemporaries using internal fixation combined the disadvantages of operative and conservative fracture treatment by opening up the fracture focus and after operation protecting it by long-lasting immobilisation in plaster, avoiding any weight-bearing.
2. Infections and nonunions after internal fixation were quite frequent.
3. Lack of comprehensive surgical armamentarium.

The AO Venture

In 1958 I was privileged to host a meeting of some 15 general and orthopaedic surgeons to discuss the reasons for the rather poor results of conservative as well as of operative fracture treatment in our country. The starting point of this group, which later developed into the so-called AO (*A*ssociation for the study of *O*steosynthesis; in English speaking countries ASIF: *A*ssociation for the *S*tudy of *I*nternal *F*ixation), was the clear insight that there was a problem and that it might be solved by careful group effort. The meeting was initiated by Maurice E. Müller, who had spent some time with Danis and immediately grasped the tremendous potential of his compression fixation of fractures, avoiding external fixation, and allowing early pain-free active mobilisation. Wasn't the "soudure autogène" of Danis the very thing E. F. Cave had been looking for as an index of perfect alignment in treatment of fractures when he said: "The more accurately a fracture is aligned, the less demand there will be for callus" (p. 49).[9]

The work of pioneers such as Lambotte, Danis, Küntscher, and others was conclusive enough to demonstrate good basic tolerance of either compression fixation or medullary splintage by human bone. Was there a way to increase the reliability and reproducibility of good results by the average trauma surgeon? It seemed clearly necessary first to define the basic principles of such successful internal fixation and to find out how best to avoid its pitfalls. Four principles seemed clearly instrumental for obtaining optimal results and we accepted them as "working hypothesis":

anatomical reduction
rigid internal fixation
atraumatic technique on *soft-tissue* as well as on *bone*
early pain-free active mobilisation, especially during the first 10 postoperative days

To prove or disprove this hypothesis, efforts in three directions seemed essential:

animal experimentation on the pathophysiology of bone repair under various biomechanical conditions with and without internal fixation
creation of a comprehensive armamentarium taking advantage of modern technology

careful clinical follow-up in patients treated for fresh fracture nonunions and malalignment.

Pathophysiology of Bone Repair

The following facts have been established beyond doubt:

1. Cortical bone after fracture or osteotomy, held together rigidly by compression fixation, is able to heal on the basis of "haversian remodelling": intense perivascular osteoblastic and osteoclastic activity leads to remodelling of the haversian osteones. Sprouting of such vessels across the fracture line with perivascular ossification welds together the fragments leading to so-called "primary bone-healing" (Schenk and Willenegger).[39] Thus the radiological observations of Danis described as "soudure autogène" were confirmed by extensive histology in various animal species (rat, dog, horse) and in man (Perren et al.[21] and Rahn et al.[25]).

2. A plate fixed to the bone under traction will compress the underlying bone by an equivalent compressive force. Strain gauges were used to monitor magnitude and maintenance of forces in such a configuration in the living animal over several months. Static loads up to 300 kg pounds per cm^2 are tolerated by cortical bone without necrosis. These pressures decrease only very slowly over several weeks. The fall in pressure seems to parallel the haversian remodelling which obviously replaces the "pressure loaded osteones" by new ones. The experimental set-up is such that bone resorption of 10 μ would lead to immediate abolition of pressure. It can be concluded that there is no such thing as pressure necrosis due to static forces almost up to the point where bone explodes. Internal fixation therefore may benefit from the engineering advantages offered by compression to stabilize bone fragments (Perren et al.).[22, 23]

3. Pressure as such has no "osteogenic effects." It only helps to set the stage for ossification to proceed optimally by eliminating interfragmentary micromovements.

4. If dynamic load changes on a "bone-implant complex" are greater than the static preload given to this complex, relative micromovements between implant and bone may result. Such micromovements inevitably lead to bone resorption. What has been considered to be pressure necrosis is therefore nothing else other than reaction of bone to micromovement between bone and implant or between bone fragments (Perren et al.).[22, 23] A similar biomechanical constellation prevails when an aneurysm is pounding on a bone surface at every pulse wave.

5. The amount of "stress-protection" of bone under conditions of internal fixation seems to be critical. Too much fixation may completely suppress the physiological stimulus of weight-bearing and movement. Osteoporosis of the "idle bone" results. This process is reversible but may lead to fatigue fracture shortly after removal of the implants or if internal fixation is excessive as, for example, in double plating of the diaphyseal bone. Insufficient stability, on the other hand, permits micromovement and leads to bone resorption, irritation callus, and quite often to fatigue fracture of the implant. The optimal internal fixation would be one that prevents all relative movements of fragments in the whole fracture area, but retains normal elasticity of the reconstructed bone. No method of internal fixation completely fulfills these postulates. The ideal of complete cortical reconstruction, prevention of relative interfragmentary movements, and avoidance of too much stress protection should be constantly kept in mind when carrying out internal fixation.

6. Infection, although highly undesirable after internal fixation, does not necessarily interfere with primary bone healing as long as vascularity of the bone and stable interfragmentary contact is maintained (Rittmann and Perren).[26] Hence, as long as implants provide stability of vascular bone, they should be left in place even in the face of infection!

Creation of a Comprehensive Armamentarium

The creation of the many implants and instruments would be a story in itself. Suffice it to say that Maurice E. Müller, in collaboration with Robert Mathys, basing their development on Danis' pioneer work, designed an instrument set to be tested and modified by the group. Most of the developments, however, came from sys-

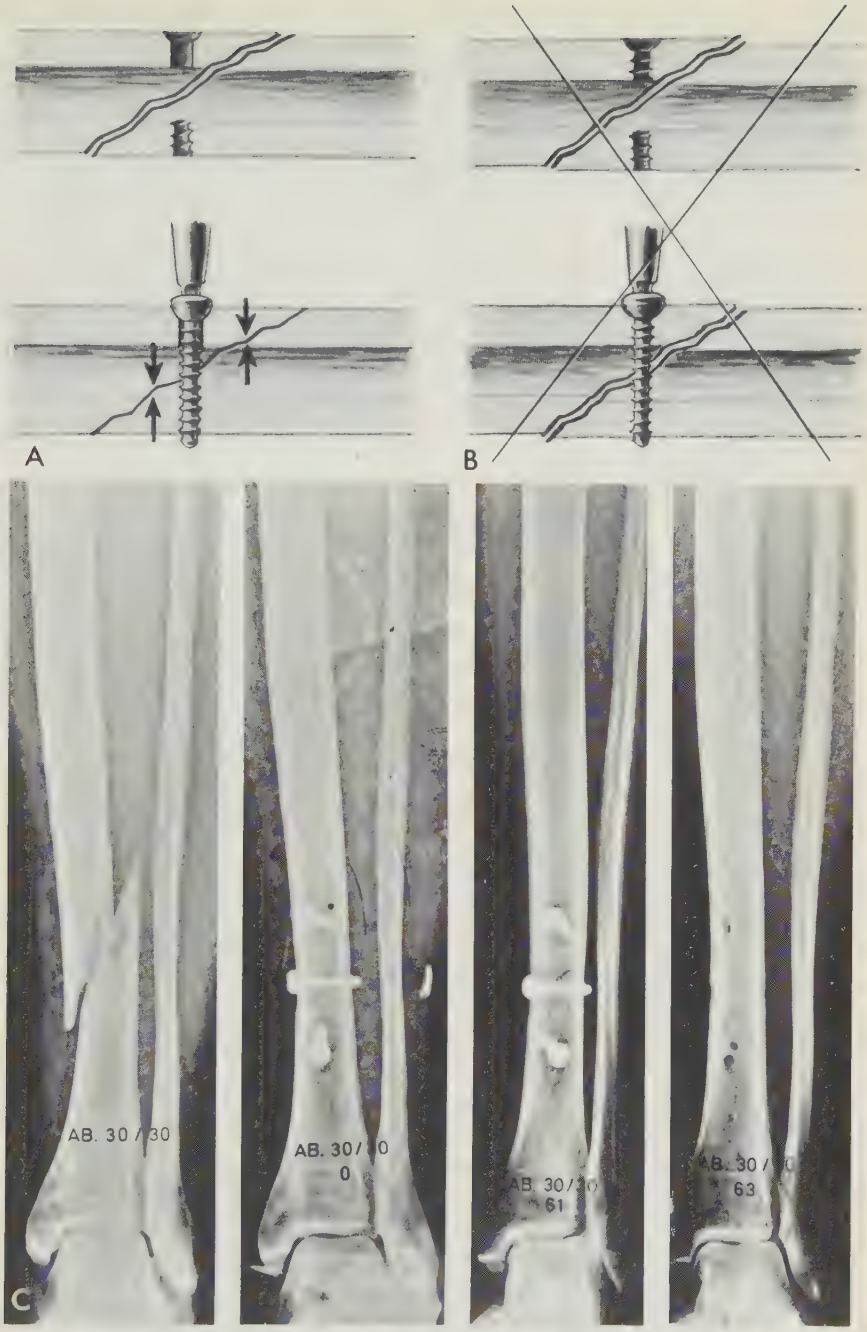

Figure 1. *A*, A lag screw, when tightened, creates compression between the fragments in cortical bone. To this effect the proximal screw hole is drilled to the outer diameter of the thread so that the screw glides in it (gliding hole). The screw holds only in the opposite cortex, which is drilled to the inner diameter of the screw and then threaded by means of a tap (threaded hole). Tightening of the screw compresses the fragments. *B*, A screw holding with its thread in both fragments cannot exert compression. (*From* Müller, M. E., et al.: Manual der Osteosynthese. Ed. 2, Springer Verlag, 1977, with permission.) *C*, Isolated distal tibia facture with varus tendency successfully fixed by means of cortical lag screws. Note the "primary bone healing" without radiologically visible callus.

tematic tests of various implants on dead bone as well as on living bone in experimental osteotomies in the rabbit, the rat, the dog, and the sheep. Starting with a basic set of instruments and implants of about 200 items, nowadays the whole armamentarium includes some 1400 items.[19, 20]

Stable internal fixation can be accomplished by two basic principles. The first is *interfragmentary compression* by means of lag screws (Figs. 1 and 2), compression plates, and tension band wires. (The word "compression plate" is a misnomer because the plate, in order to compress the bone, is put under tension! However, the suggestive term of compression plate has entered the surgical vocabulary for good!) The other principle consists of *intramedullary splinting by a nail.* In 1958, these two basic possibilities were available in many different sets of instruments, most of them rather crude from a mechanical standpoint and all of them metallurgically incompatible. It therefore seemed paramount to take the best available features and create an integrated set of instruments which would allow the surgeon to tackle every fracture. "Narration" of the development of our medul-

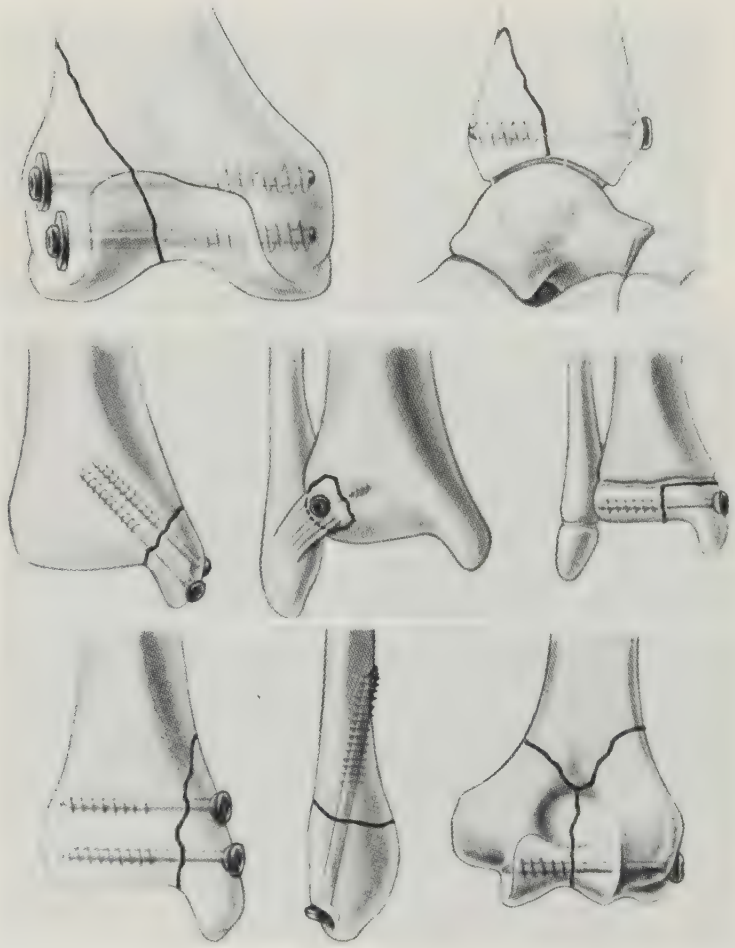

Figure 2. In cancellous bone, the lag effect can be realized by screws with relatively thin shafts, the thread anchoring in the opposite fragment. (*From* Müller, M.E., et al.: Manual der Osteosynthese. Edition 2. Springer Verlag, 1977, with permission.)

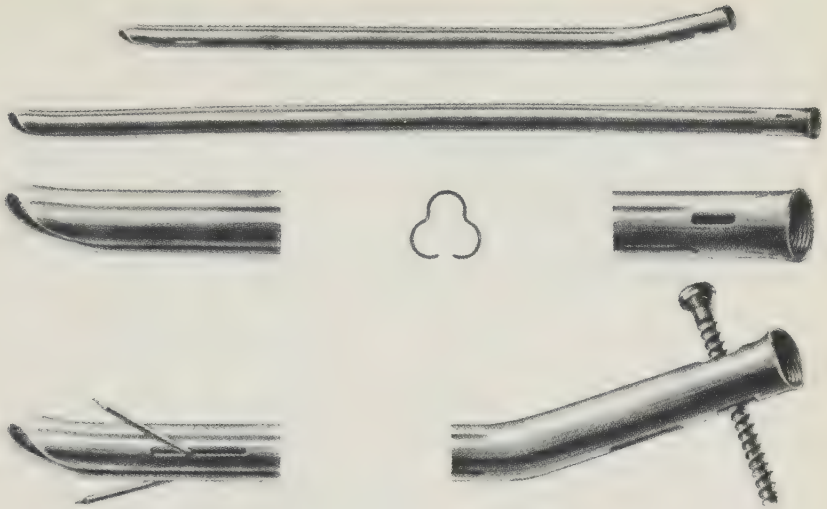

Figure 3. Medullary nail with inner thread at the upper end, a proximal slit (for antirotational stabilization by means of a screw), and a distal slit (for insertion of antirotational K wires). (*From* Müller, M. E., et al.: Manual of Internal Fixation, Springer Verlag, 1970, with permission.)

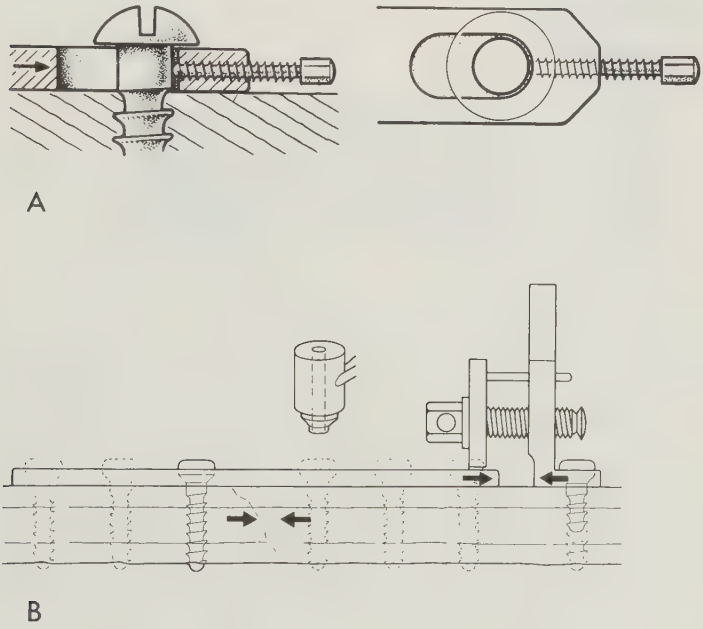

Figure 4. *A*, Danis plate with compression mechanism welded to the plate. Tightening of the compression screw pulls on the plate fixed to the opposite fragment and hence compresses the fracture axially. *B*, Plate with removable compressor designed by M. E. Müller. (*From* Allgöwer, M., et al.: The Dynamic Compression Plate (DCP). Springer Verlag, 1973, with permission.)

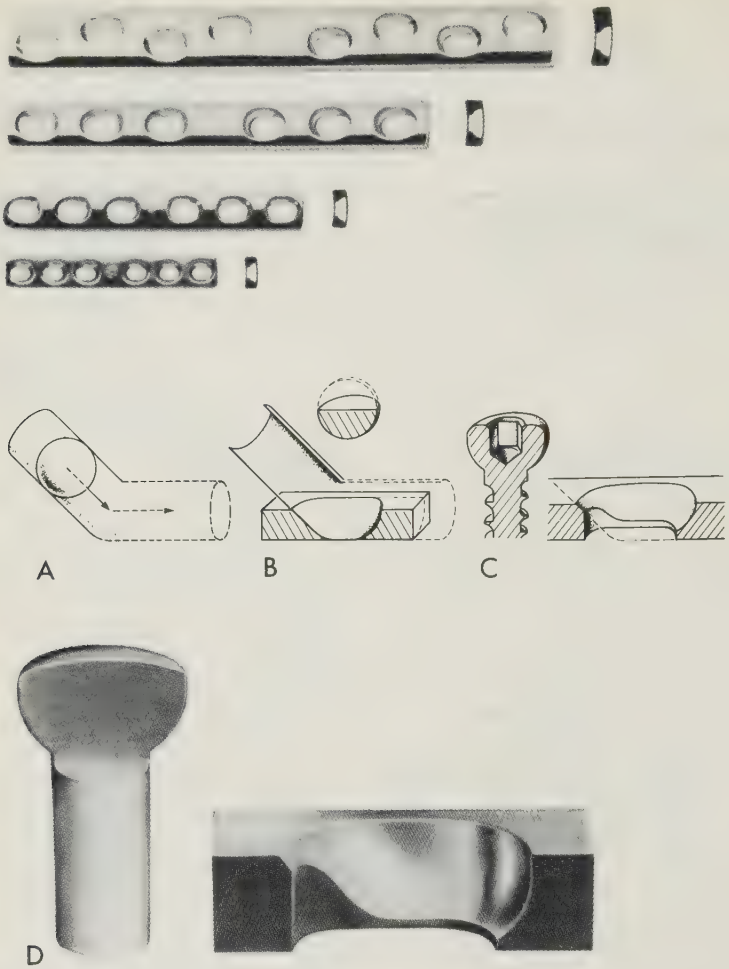

Figure 5. *Top,* Broad dynamic compression plate, narrow dynamic compression plate, 3.5 mm dynamic compression plate, 2.7 mm dynamic compression plate.

Bottom, Schematic representation: the new screw hole, which permits compression of the osteotomy (or fracture) when the screw is driven home, offers adequate stability and prevents any locking effect. *A,* A ball (screw) is guided into a sloping cylinder (screw hole). Any downward movement will result in horizontal displacement. No lateral movement is possible. The position aimed at is the intersection of the two cylinders. This position offers maximal stability without any locking effect. In the horizontal cylinder, displacement towards the osteotomy is possible. *B,* Projection of the cylinders into the screw hole and the half-shaped screw. *C,* Actual shape of the hole with the slot necessary for the screw neck and thread. *D,* The spherical countersunk screw head is congruent to the hemicylinders constituting the screw hole in any position. Longitudinal section through the screw hole of the dynamic compression plate and through the screw head of the dynamic compression plate. (*From* Müller, M. E., Allgöwer, M., and Schneider, R., et al.: Manual der Osteosynthese. Edition 2. Berlin, Springer Verlag, 1977, with permission.)

lary nail and the basic designs of our compression plates will serve to illustrate our approach.

At the outset, there were two kinds of medullary nails available, each having several advantages and disadvantages. Küntscher's tibial nail with its clover-leaf profile gives good rotation stability. It proved to be rather rigid, especially with

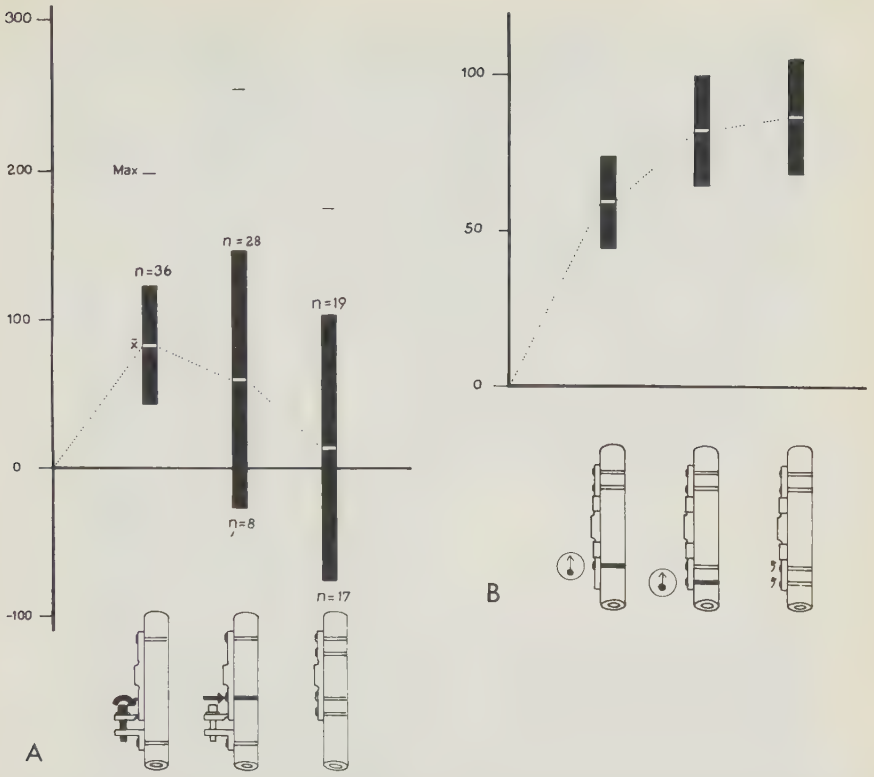

Figure 6. *A*, A group of 36 skilled surgeons used a removable tension device to apply compression to an intact femur by means of round hole compression plate with circularly fitting screw holes. The initial compression and subsequent changes after insertion of all the screws and removal of the tension device were measured. The average initial compression is around 80 kp and shows a wide spread of values. Introduction of the first screw reduced the compression to about 60 kp and resulted in a wider spread of values. In eight cases "negative compression" (= distraction) was found. At the end of the experiment the average compression value was only 14 kp. In 17 cases no compression was retained. The reason for these changes is a slight unavoidable eccentricity in placement of the screw holes, which results in large changes in compression in a comparatively rigid system. (*From* Allgöwer, M., et al.: The Dynamic Compression Plate (DCP). Springer Verlag, 1973, with permission.)

B, Similar experiment as in 6*A* using a dynamic compression plate. The initial compression achieved with one screw positioned with the load guide is 60 kp; positioning a second screw with the help of the load drill guide increases compression. Final tightening of the screws results in a slight further increase. (*From* Allgöwer, M., et al.: The Dynamic Compression Plate (DCP). Springer Verlag, 1973, with permission.)

increasing diameter. Herzog created a tibia nail with a physiologic curvature proximally and with openings distally, permitting the insertion of antirotational wires in unstable tibia fractures. In Küntscher's as well as in Herzog's nail, it is difficult to apply a really central thrust when driving the nails in, and particularly when removing them after bone healing. We therefore designed a nail with an inner thread at the upper end. This small improvement makes all the difference in the easy handling of the nail at insertion and extraction. Furthermore, by varying the thickness of the wall with increasing diameter, the elasticity of the various nails was largely equalized (Fig. 3).

Another interesting story is the development of various compression plates (Figs. 4 to 7). In Danis' famous compression plate the compressing mechanism is welded to the implant itself. This creates great metallurgic hazards. Müller solved

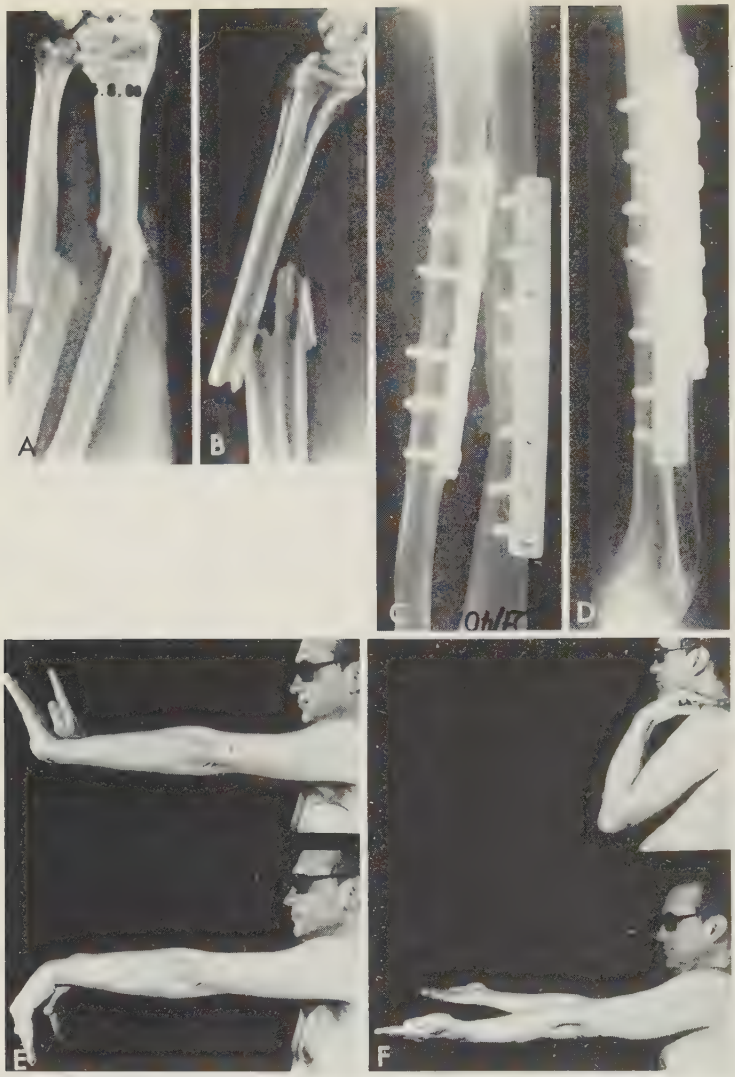

Figure 7. Open forearm fracture fixed by self-compressing (dynamic compression) plates. Immediate postoperative mobilization without any external fixation. Complete functional recovery.

the metallurgical problem very elegantly by designing a removable compressor. However, the round hole of our first plate with a rather precise conical geometry between plate hole and screw head has certain drawbacks. Slight eccentricity of screws introduced after the initial compression-procedure abolishes the initial compression or even leads to distraction of the fragments. Furthermore, the removable compressor requires extra exposure, which means a larger wound. Bagby,[6] using an old carpenter's principle, had developed a self-compressing plate. The conical screw head dislocates the plate when driving home the screw, thus inducing axial compression in the bone. In Bagby's system, however, there is only a one point contact between screw head and plate. Instability can result very easily. Together with Perren and Russenberger, the present writer devised the so-called

dynamic compression-plate (DCP^R), introducing the spherical gliding principle.[2, 24] This plate realizes a spherical geometry between plate hole and screw head. Apparently design and designation of the dynamic compression plate seems very suggestive, because they were closely followed in America by the UCP (universal compression plate) or the SCP (self compressing plate). Both these plates look very similar to the DCP, however they are simply modified Bagby plates. Since the design is such that only one point contact between plate and screw-head is achieved during the procedure of compression by the UCP and the SCP, they do not incorporate the spherical gliding principle of the DCP.

Two interesting spin-offs of the initial DCP were miniaturized DCP's for maxillofacial surgery by Spiessl and his group[42] and for hand surgery by Heim and Pfeiffer[15] and by Segmüller.[40] There is probably no other part of the body more susceptible to fracture disease than the hand, if it remains in pain and is immobilized by external splinting. Fractures of the phalanges and of the metacarpals have become amenable to internal fixation using the same principles as in large bone. This allows immediate pain-free postoperative mobilisation. By this very fact, the incidence of so-called Sudeck's atrophy of the hand has greatly diminished.

The development of new designs in implants and of new instruments would not have been possible without the previous testing in the laboratory of experimental surgery at Davos and without continuously checking the clinical results at the Documentation Center which was established in Berne. Progress in instrumentation would have been impossible without the devoted help of Robert Mathys, who constructed the many experimental models and indefatigably carried out the requested modifications. Fritz Straumann provided the metallurgic know-how. His institute also helped to construct various implants and instruments and kept a very tight quality control on the raw material as well as on the finished implants and instruments.

The Davos Spirit and the Davos Dilemma

At the outset, we were aware of the inherent danger of the more aggressive approach to fracture treatment. We therefore decided that we would only produce enough instrument and implant sets for the group of surgeons involved in the initial tests. Our concern was not to let the system fall into disrepute by misuse before testing it thoroughly. This went very well at the beginning. No sooner had "successful cases" gone out of our hospitals, than other surgeons became anxious to avail themselves of the same instruments. Our refusal to comply with those wishes was resented by some rather bitterly. When we presented for the first time the results of our cooperative study at the occasion of a meeting of the Swiss Surgical Society in November 1960, two kinds of reaction were clearly audible. There were those who considered this aggressive group of surgeons as to be far too knife-happy and predicted a bitter end. There were others who were deeply resenting the fact that the system was not freely available, accusing us of monopolizing the system for our own benefit.

We therefore decided to make the system available to those surgeons willing to invest the necessary time for an instructional course at Davos. This was probably one of the most fruitful and rewarding decisions we ever made. Initially conceived as a very temporary institution, these courses have become traditional, and much to our surprise, have remained oversubscribed over the years. Moreover, such courses have been in demand in a number of other countries.

We make it a point to stress that such courses do not propagate the indiscriminate use of internal fixation, but rather caution the surgeon against its many pitfalls. The surgeon should be enabled to select and carry out a reliable method in cases in which he feels internal fixation is indicated. Modern teaching aids, especially television, have permitted relatively large laboratory sessions, where surgeons grouped in teams of two carry out various procedures on preserved bones. In some 55 courses, more than 10,000 surgeons were able to study and evaluate for themselves the implants and instruments developed over the years and familiarize themselves with their use.

If a group effort creates an income, it also creates ethical problems of the surgeons involved in devising the instruments. Initially, we did not anticipate that our instruments should create more than a modest profit, enabling us to keep the research unit in Davos and a documentation center at Berne going. Originally, these institutions had to be financed from our own pockets and we even had to guarantee the bills for the raw materials needed for the fabrication of implants and instruments. After some tough years, draining us individually of a lot of money, the easier years arrived. Finances improved such that we were able to equip quite well the centers at Davis and Berne and also provide additional research money for other scientific institutions. Fortunately at the outset, a gentlemen's agreement had established the strict rule that any income created by the instruments would be reinvested into research and documentation. Thus the AO organisation (ASIF) has remained strictly noncommercial, as the surgeons involved have no material interest, but are only decision-makers.

An organization, to which financial responsibility could be delegated had to be founded and funded—that's how the shareholder company of Synthes was founded with the explicit agreement that never more than 5 per cent should be paid on the share capital of 50,000 Swiss francs! Thus the shareholders could be sure that any money earned from Synthes activity could be reinvested into documentation, research, and teaching. By a gentlemen's agreement, the shareholders have no personal share in the earnings of the society apart from some fixed compensation for their personal engagement in time and money during the last years. Thus not only the AO group, but also Synthes Chur, the licensor of all ASIF implants and instruments, is run as a nonprofit organization. It is quite obvious that although the earnings are not going to "private pockets," it is without any doubt a great privilege to have money available for research and travelling, which can be distributed without red tape. The major part of the royalty earnings is earmarked for the research laboratory at Davos and the documentation center at Berne. Further research money goes on to Berne, Basel, St. Gallen in Switzerland, Altdorf, Homburg, Mainz, Ulm in Germany, and in recent years to countries outside Europe as well as surgical fellowships from and to Switzerland. In view of the international impact, an international programme of education seemed paramount. AO International was founded and funded to coordinate postgraduate teaching on an international level. During the last 15 years a royalty income of some 32 million Swiss francs has been created and reinvested in education and research.

Clinical Follow-up

Our documentation center by now has some 30,000 cases of internal fixation on files. We were not as yet able to extract the host of information contained in this important documentation. We already have learned a lot from these clinical cases, in particular that success or failure of internal fixation are predictable immediately after operation in the large majority of cases. We have a good overview with regard to early results like infection rate, hospital stay, etc. With regard to infection rate, we may take the most critical and controversial bone—the tibia. In 4440 operated tibias, including some 10 per cent of compound fractures operated by the group, the infection rate was 1.9 per cent.

Table 1. *Collective AO Review of Forearm Fractures*[31]

FUNCTIONAL RESULT*	CASES	PER CENT
Good	114	86
Acceptable	15	11
Poor	4	3
TOTAL	133	

**Good*, functional recovery compatible with normal professional and extraprofessional activities; *acceptable*, bony healing, union, moderate functional restrictions; and *poor*, nonunion, major impairment of pronation and supination.

Table 2. *ASIF Compression Plating of Forearm Fractures: The Campbell Clinic Experience from 1960–1970*[4, 30]

	HEALING RATE	
	CASES	PER CENT
Forearm fractures	258	97
Forearm pseud-arthrosis	62	96

Meaningful documentation of fracture sequelae, however, requires follow-up over several years. Despite considerable investment in time and money, cooperative documentation of late results proved more difficult than we anticipated. We are still working on this problem. In our own institution, we were fortunate (and stubborn enough) to have consecutive series with a near 100 per cent follow-up of patients with a variety of fractures and they shall briefly be discussed.

Fractures of *forearm bones* in adults have been known for the rather poor results with conservative as well as with unstable operative treatment (for example, pinning). For these fractures, compression plating has become rather universally accepted. In our own institution the results are demonstrated in Table 1.[31] Anderson,[3, 4] from the Campbell Clinic using on the whole rather short ASIF compression plates, was able to duplicate these results (Table 2). In fractures of the femur, treatment in suspended traction is possible, but rarely is there complete recovery of knee flexion. Internal fixation by plating in connection with medial cancellous onlay graft or medullary nailing allows right angle positioning of the operated leg, preventing pathological adhesions of the quadriceps to the femur. Early postoperative mobilisation normally leads to complete knee movement within 2 to 3 weeks after injury, a finding which is quite at variance with previous results. Our follow-up in a series of 131 cases yielded the results given in Table 3.

Schatzker[37, 38] compared results of conservative or partial operative treatment with stable internal fixation in condylar and supracondylar femur fractures and in fractures of the tibial plateau and found the significant results given in Tables 4 and 5.

Distal tibia fractures with involvement of the complex tibiotarsal joint very easily develop post-traumatic arthrosis. A series of 155 patients evaluated at a minimum of 4 years after operation (Rüedi et al.)[29, 30] bears out the point that results of internal fixation are mostly predictable. Fractures reduced anatomically return to normal function, occasionally after rather long periods of time. Even if still somewhat handicapped at three years, they tended to improve further over the years. There is no mystic factor leading to post-traumatic arthrosis other than poor anatomic alignment or severe damage to the cartilage (Fig. 8 and Table 6).[32]

Table 3. *Two Year Results of 131 Consecutive Comminuted Femoral Fractures Treated by Self-Compressing Plates DCP in Combination with Medial Cancellous Onlay Grafts*[33]

RESULTS*	CASES	PER CENT
Good	115	88
Acceptable	9	7
Poor	2	1,5
Died	5	3,5
TOTAL	131	

**Good*, functional recovery compatible with normal professional and extraprofessional activities; *acceptable*, knee-flexion >90°, extension <–5°, normal professional activities, extraprofessional activities reduced; and *poor*, any handicap more than under "acceptable."

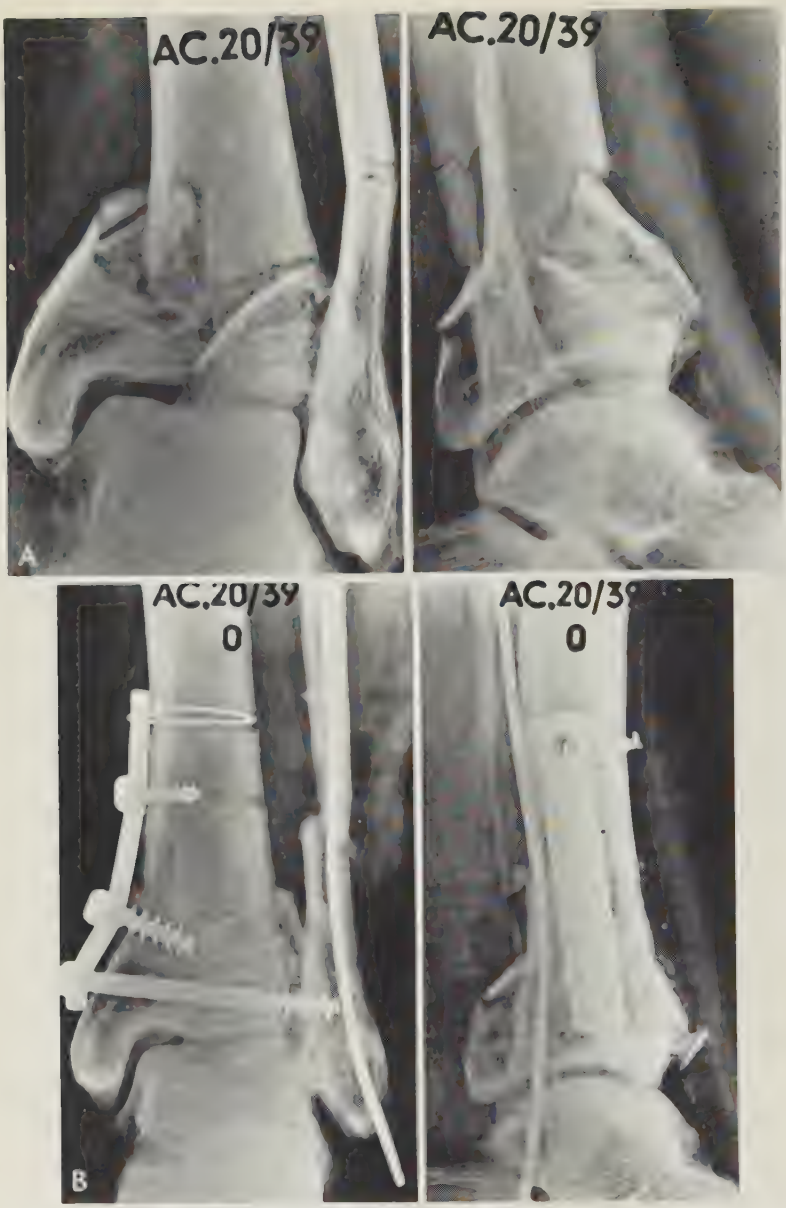

Figure 8. *A* and *B*, Fracture of distal tibial joint treated by four basic principles: fibular reconstruction, reconstruction of joint surface, filling of cancellous bone defect by autologous cancellous bone, and medial support to prevent secondary varus deformation. This case was published about one year after operation. By mistake this patient had walked in his caliper almost a year. This led to extreme decalcification and to changes of the cancellous structure that are still visible 458 weeks after operation. However, he has had a complete functional recovery with no post-traumatic arthrosis, and he has been back at work as ski instructor for 15 years.

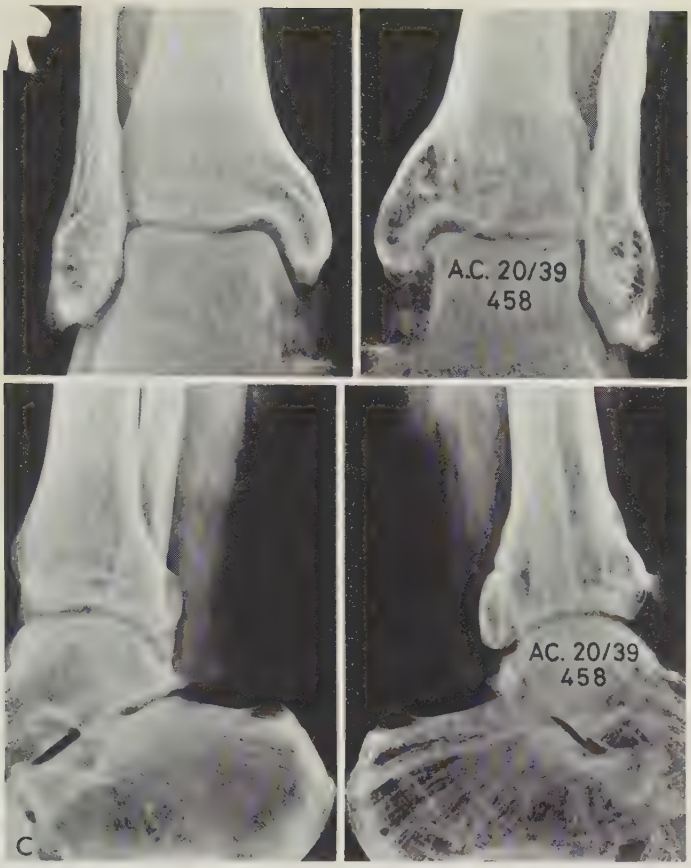

Figure 8 *Continued.* C, Aspect 458 weeks (almost nine years) after operation.

Table 4. *Supracondylar Fractures of the Femur*[*37]

	NO.	EXCELLENT	GOOD	FAIR	FAILURE	GOOD TO EXCELLENT (PER CENT)
All cases	35	4	13	9	9	49
AO method	17	4	8	5	0	71
Other	18	0	5	4	9	21

**Excellent*, full extension, flexion loss <10°, no varus, valgus or rotatory deformity, no pain, perfect joint congruency; *good*, not more than one of the following: loss of length not more than 1.2 cm. <10° varus or valgus, flexion loss not more than 20°, minimal pain; *fair*, any two of the criteria in good category; and *failure*, any of the following: flexion to 90° or less, varus or valgus deformity >15°, joint incongruency, disabling pain no matter how perfect the x-ray.

Table 5. *The Tibial Plateau Fracture: The Toronto Experience from 1968 to 1975*[38]

	CONSERVATIVE	SURGICAL
Acceptable	22 (58%)	25 (78%)
Unacceptable*	16 (42%)	7 (22%)
TOTAL	38	32

**Unacceptable*, any of the following: flexion <90°, significant knee instability, pain, and significantly reduced work tolerance.

Tibia fractures are the most frequent, socially the most important, and therapeutically the most controversial fractures. In 1963 Müller, Allgöwer and Willenegger[18] published their first comprehensive book on internal fixation. In this book, we reproduced the x-ray follow-up of every case in a consecutive series of 188 tibia fractures, treated by internal fixation.[1] Two more such series were carefully followed by Mrs. E. Segmüller,[40] investing over one year of hard work in locating every single one of a very mixed patient population who had come to ski in our area from all over the world (Table 7). She was able to show that stable internal fixation and immediate postoperative mobilisation in these 617 operated tibia fractures had led to complete restoration of function in the large majority of cases—a finding quite at variance with what had been customary in our country at that time. Ten years later, Rüedi evaluated a consecutive series of closed and compound tibia fractures treated operatively again with a 100 per cent follow-up (Tables 8 and 9).[34] These series concerned a city population with more traffic accidents than the previous one, a higher average age of patient, and a higher number of operating surgeons. The end result, despite some early complications, may be considered extremely satisfactory.

We are not particularly anxious to advocate internal fixation for tibia fractures. Our data only should demonstrate that internal fixation in tibia fractures can be done without too much of a hazard to the patient, provided there is continuous involvement of experienced consulting staff in every single case.

Compound fractures have been a contraindication to internal fixation for many surgeons and immobilisation by plaster mandatory. Rittmann[28] has recently looked at the result of 214 compound fractures treated 4 to 10 years previously by early operative stabilisation. He and his collaborators were able to achieve a 100 per cent follow-up at the price of travelling to Italy and Spain to find those patients usually "lost to follow-up"! With an initial infection rate of 7 per cent, 4 to 6 years later infection had been successfully overcome in all cases (Table 10). In third degree

Table 6. *Comparison of Overall Result (Subjective and Objective) after Pilon Tibial Fractures*[32]

RESULTS	1968 TO 1969* n = 80	1977† n = 75
No complaint or pain ± symmetric range of motion‡	73.7%	69.4%
Occasional pain or discomfort, range of motion minus 15° to 25°‡	11.3%	18.6%
Constant pain, very limited motion (>25°),‡ or fusion of ankle joint	15%	12%

*On average 4 years postoperative.
†On average 6 years postoperative.
‡Summation of loss of motion in tibiotalar joint.

Table 7. *Results of 617 Fractured Tibias Treated by Stable Internal Fixation**

FRACTURE			LATE DISABILITY (NONE > 20%)	
Site	Type	Number of Cases	n	%
Shaft of tibia	closed	535	6	1.1%
	compound	45	8	17.7%
Distal tibia	intraarticular	37	3	8.1%
	TOTAL	617	TOTAL 17	2.7%

*Total of 4 fully controlled series: 1958/59, 1959/60, 1961/62, 1962/63. No case received insurance compensation for permanent partial damage of more than 20 per cent (total invalidity being taken as 100 per cent).

injuries, use of external fixators anchoring in the bone has rightly become popular because of minimal additional interference with blood supply to the area of injury. External fixators provide enough stability to permit early mobilisation and therefore fulfill the most important criterium postulated for internal fixation.[27]

Nonunions are best treated by solid "biomechanical" stabilisation without removal of the "fatigued, interposed tissue." Twenty years back, it was generally held that a nonunion would need as many months of external fixation as a fresh fracture weeks. Weight-bearing very often was prohibited completely. This almost invariably led to irreversible reduction in the range of movement of adjacent joints. With modern internal fixation, surgical treatment of nonunions usually takes only a few days in hospitalisation and needs no external fixation. The patient regains mobility and muscular strength during the time where the bone is healing, undisturbed from mechanical interference thanks to stable internal fixation (Fig. 9 and Table 11).[44]

Not everything in trauma is fracture. Fatalities in trauma are most often due to multiple system injury, leading to multiple organ failure with respiratory distress syndrome at the beginning and liver and kidney failure at the end of a vicious circle. The fact that we were able to practically eliminate the so-called trauma lung and the consecutive other organ failures is felt to be due to two prophylactic measures: *aggressive cardiorespiratory treatment and early internal fixation of proximal long bones.*

Where Are We 20 Years Later?

Three statements may be made: (1) There is an armamentarium at hand to deal surgically with practically all fractures. This has proven important especially in

Table 8. *Follow-up of 435 Consecutive Tibial Shaft Fractures with DCP Fixation*[34]

	FRACTURE					
	Closed		Open		TOTAL	
DCP fixation	334		101		435	
Follow-up	323		95		418	
Personal		300		88		388
X-ray and questionnaire		23		7		30
No control	2		—		2	
Died	9		6		15	

Table 9. *Functional Results 1 to 2 Years After DCP Fixation of Fractures of the Tibial Shaft*[*34]

RESULTS	CLOSED FRACTURES		OPEN FRACTURES	
	Cases	Per Cent	Cases	Per Cent
Good	317	98	84	88.5
Acceptable	6	2	8	8
Poor	—		3	3.5
Total	323		95	

*Good, functional recovery compatible with normal professional and extraprofessional activities; *acceptable*, occasional complaints (pain, fatigue), normal professional and reduced extraprofessional (sports) activities; and *poor*, any of the following: significant pain in tibiotarsal or knee joints, reduced professional activities, nonunion, amputation.

the weight-bearing joints of the leg, in the forearm bones, and more recently in fractures of the hand and the foot. (2) Fracture disease is preventable unless there is extensive tissue destruction. In fact, fracture disease has virtually disappeared from our fracture series. (3) Infection rate in operated closed fractures (0.5 to 1.5 per cent) and compound fractures (about 7 per cent) is reasonably low. Still it remains the major concern with regard to internal fixation. Infection, however, can be treated successfully in almost 100 per cent of the cases by the combination of four therapeutic elements. In order of efficacy they are: (1) maintenance or reestablishment of stability; (2) careful debridement of all dead tissue in freshly operated fractures and removal of dead bone in chronic infection; (3) filling-in of bone defects by cancellous autotransplant; and (4) antibiotics.

Is there widespread acceptance of the AO/ASIF method? The answer is yes and no! This is best illustrated by the response of our guests of honour at the Davos courses. At each of these courses we invite a guest of honour known for his achievements in the surgery of locomotor system and trauma. The main commitment of such a guest consists in a critical evaluation of the course at its end. Up to now, the list of names includes W. Bickel/Rochester, L. Böhler/Vienna, H. B.

Table 10. *Late Results in 200 Consecutive Patients with 214 Compound Fractures Treated Between 1967 and 1971 (Tibia 131, Femur 22, Forearm 19, Humerus 16, Others 26)*[*28]

DEGREE OF INJURY	DEATH			OSTEITIS		OSTEITIS HEALED AFTER:			AMPUTATIONS
	No.	Related to Accident	Reported Dead at Follow-up	Early	After Leaving Hospital	1 Year	1–3 Years	3–6 Years	
I	88	1	13	1	1	1		1	
II	93	4	5	2	3	2	3		1 late, due to arterial disease
III	31	0	2	5	2	1	2	2	5 immediate, 2 late, osteitis

*Seven patients reported dead at 2 to 4 years follow-up from unrelated causes, 13 patients reported dead at 6 to 10 years follow-up had age average of 70 and died 4 to 6 years unrelated to accident. In 175 patients alive at 6 to 10 years follow-up, all infections seemed eradicated with two late amputations due to extensive tissue damage and osteitis.

Table 11. *Summary of Results of Internal Fixation in Nonunions (Partially in Combination with Cancellous Autotransplantation)*[44]

LOCATION OF NONUNION	NUMBER	HEALED
Clavicula	18	16
Humerus	45	44
Forearm	46	46
Femur-neck	23	21
Pertrochanter	5	5
Femur (shaft)	134	131
Patella	3	3
Tibia aseptic	127	126
Tibia septic	122	117
TOTAL	523	509 (97%)

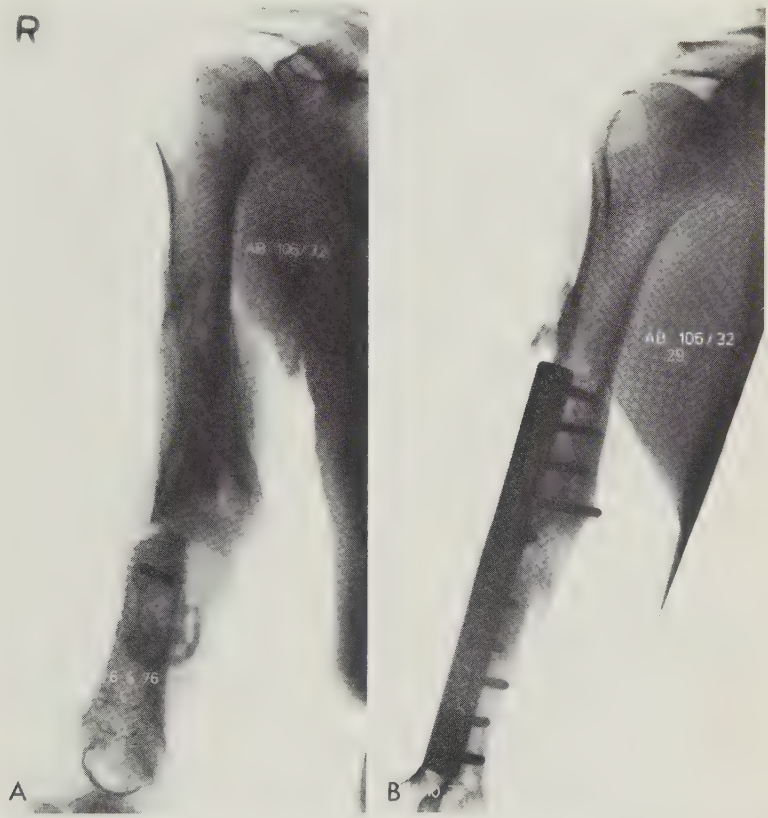

Figure 9. *A*, Nonunion of humerus of three years duration after several surgical attempts at stabilization, finally considered beyond surgical repair and fitted with a heavy orthopedic splint in an internationally known trauma center. *B*, Radiologic appearance 28 weeks after rigid compression fixation by means of a large self-compressing plate with immediate postoperative mobilization, 10 days of hospitalization, and no external fixation. Complete functional recovery resulted.

Boyd/Memphis, J. Charnley/Wrightington, R. L. Cruess/Montreal, A. B. Ferguson/Pittsburgh, W. T. Fitts/Philadelphia, C. Hirsch/Göteborg, K. Jansen/Hellerup, C. Kallio/Helsinki, H. J. Mankin/Boston, R. Merle d'Aubigné/Paris, H. Osmond-Clarke/London, R. A. Robinson/Baltimore, O. Scaglietti/Firenze, A. Trillat/Lyon, C. P. van Nes/Leiden, P. A. Wade/New York.

Dr. Cruess from Montreal in 1974 has probably given the most succinct evaluation of the "general feeling" among these critical minds. He said:

"We feel, as I am sure most of you do by now, that the AO-group has produced the most outstanding integrated set of instruments which has ever been offered to the orthopaedic profession and to the patients under their care. The use of these tools requires a complete knowledge of the system and of its meticulous techniques.

"The first bit of advice which is offered to my fellow North American orthopaedic surgeons is as follows: It is not necessary to utilize the AO-approach to every fracture, but if rigid internal fixation and early mobilisation are selected as a method of choice and if the AO-instruments are to be used they must be inserted as recommended by the AO-group.

"The second point which I believe deserves great emphasis deals with the AO-approach to the periosteum and soft tissues. If the periosteal dissection of all fractures is carried out in conjunction with massive use of internal fixation, avascularity of large areas of cortical bone will result, there will be large dead-space and fracture-healing will be retarded rather than proceed at a satisfactory rate.

"I would like to address a few remarks to my friends and hosts in the AO-group: We still have unanswered questions: Cancellisation of cortical bone under the plate. Does a rigid plate whose modulus of elasticity is markedly different from that of bone lead to faster and better union or should newer materials which more closely approximate bone be under investigation?

"How are we, as responsible members of the medical community, to select an operative or non-operative approach to given fractures when in the literature we read articles by reputable individuals whom we respect, which on the one hand stress the so-called fracture-sickness and the benefits of internal fixation and on the other we read of contemporary non-operative fracture-treatment which also stresses early function, early mobilisation of joints and tells us the end-results are gratifying to the patient and surgeon. Both approaches have their catastrophes, their failures and their successes. I therefore urge the AO group now that they have established rigid internal fixation as a recognized method of treatment to institute prospective studies comparing modern non-operative treatment by well-trained individuals with modern operative treatment in the areas of controversy."

Taking this advice, our group from St. Gallen has in fact instituted a prospective comparative study between the new tendency in conservative treatment, instituted by Dehne[12] and Sarmiento[36] of cast bracing in tibia fractures. They found this procedure to be very successful in relatively stable fractures, but inferior to internal fixation in markedly unstable tibial fractures. In those cases where the progress of conservative treatment goes only halfway to early function we feel that stable internal fixation should be chosen.

From the reaction of our guests of honour, one might assume that there is in fact widespread acceptance of the system as comprehensive instrumentation for effective internal fixation of fractures. But there is at the same time a rather clear warning to remain extremely critical with regard to indication for internal fixation.

In fact there is widespread acceptance and even some exaggerated use in Central Europe; however, there is, to my mind, too much reluctance in the United States to take advantage of the possible benefits of internal fixation. Why is it that I, as a great admirer of American achievements in surgery, usually suffer when visiting an American trauma or fracture unit, seeing too much unnecessary suffering and delay in treatment and too many "suboptimal" end results? Why does the very popular "Campbell 1971"[10] reproduce large numbers of suboptimal examples of internal fixation? Why does the very detailed *Textbook of Surgery* by Sabiston (1977)[35] which takes 2500 pages to explain the art of surgery to the American medical student and young resident, only show examples of inadequate internal fixation?

I fully understand surgeons to be very restrictive in their indication for internal fixation. One very obvious reason is the rather high infection rate in many American hospitals. Even assuming stricter rules in determining postoperative infection rates in the United States, there seems to be a difference from what we can report to the best of our knowledge. To my mind, the main reason for this infection rate is the relatively rough handling of tissues and slow operating. As assets for a career in academic surgery in the United States, the art of careful surgical technique and smooth gentle handling of tissues ranges far behind the ability to do basic research and discuss the results intelligently in public. This certainly has done much good in increasing the knowledge of pathophysiology of the critically ill. His derangements are understood and treated more systematically than in Europe. However, in the field of precarious tissue handling, particularly in trauma surgery, this attitude is certainly somewhat unfortunate. There is hardly any other tissue of the human body as unforgiving as the skin of our lower leg. There is hardly any other tissue as demanding in biomechanical planning as bone. Visceral surgery can count on many compensatory mechanisms to straighten out a "suboptimal" anastomosis—bone surgery cannot!

Another reason for poor results with internal fixation is the inadequacy of instrumentation and the lack of maintenance. Crude instruments, blunt drills, tapes, etc., all add up to unnecessary bone and tissue damage. A tight traumatizing skin suture very often sets the pace for partial skin slough. From there to catastrophe, it's a very short way.

If infection and unnecessary skin slough are valid reasons for a reasonably conservative attitude toward internal fixation, it is difficult to understand why textbooks and operation manuals should only illustrate cases of inadequate internal fixation which indeed will inevitably add new failures.

The discussion on indication for internal fixation should be as cool and "matter of fact" as possible. Although it is a trivial point, we should remember that no surgeon can refrain completely from internal fixation as well as no one would operate on all fractures. Two aspects will need to be kept in mind. The main one is that of the indication—it remains with the individual surgeon and the individual case. The decision of the surgeon will depend on the results he thinks he can reasonably achieve with his skills in his institution. The other point is that of surgical technique, that is, careful application of the sound basic principles in the procedure of internal fixation with its biomechanical consequences for the bone.

The discussion up to this time has resolved too much around catastrophes following internal fixation. It is obvious to the careful observer that the bad results are largely due to either a disregard of the atraumatic tissue technique or disregard of biomechanical and surgical principles of rigid internal fixation. On the basis of some 30,000 internal fixations documented at AO Center at Berne, we have enough evidence to know that bone can be fixed rigidly under static preload and that rigid internal fixation provides good conditions for efficient bone healing in the face of early functional normalization of the injured limb by active movements. These possibilities offered by nature can and should be used wisely!

In many countries care of the skeletal trauma has shifted from general to orthopaedic surgery. This, however, has not as yet changed the basic attitude of many university centers to look at fractures as "quantité négligeable." I would like to see in the future that orthopaedic as well as general surgical university centers—hopefully in close cooperation—will become fully aware of the challenge which lies in the treatment of trauma by modern means.

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Blood Banking

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Historical Perspective

Surgeons are usually thought of only as the major users of blood. However, they have also been major contributors to the art and practice of blood transfusion.

Necessity led to the development of a variety of techniques for performing direct transfusions, some of which required the skill of the inventor to use effectively. Crile[8] in 1907 used tiny cannulas to join donor artery to recipient vein. Subsequently many devices were developed purportedly to simplify direct transfusions and to assure the direction and volume of flow. In fact in 1928 the book editor of the American Journal of Surgery in discussing a German publication on blood transfusion remarked that, "One may almost assert that a homo medico cannot aspire to immortality in the surgical realm unless he has devised and called after his name a blood-transfusion apparatus."[3] DeBakey[21] devised the roller pump, which not only was the best of these devices but was used by Gibbon in the oxygenator system in performing the first successful total cardiopulmonary bypass.[18] For further historical details you are referred to the authoritative textbook of Kilduffe and DeBakey[21] and a more recent review by Schmidt.[28]

Clotting was a problem in the apparatus used by James Blundell, the London obstetrician, who initiated man-to-man transfusions in 1818.[20] A contemporary colleague, John Braxton Hicks, in 1868 tried to use sodium phosphate as an anticoagulant but unfortunately all the patients died, presumably from the large doses of inorganic phosphate used. It remained for another surgeon, Richard Lewisohn,[23] to ultimately completely eliminate the need for direct transfusion by his demonstration of the safety of sodium citrate as an anticoagulant in 1915. This was also to be the basis of the earliest transfusions of blood which had been stored outside of the body.

It is hard to appreciate the tremendous significance of some of the advances which are now part of accepted routine. As a student I served as a syringe-passer in a direct transfusion and well remember the blood-stained aftermath on the linens, the floor, and my scrub suit. The appearance of the first commercially available sterile, pyrogen-free blood collection equipment was almost as welcome to the house officer of the late 1930's as the relief given by sulfapyridine from the round-the-clock routine of administering antipneumococcal sera. It was still necessary to enter the collection container if one felt it desirable to remove a portion of the anticoagulant-plasma mixture to raise the hematocrit of the diluted bank blood to lessen the load of volume, citrate, and sodium given to the patient. These early attempts to use packed red blood cells (official name Red Blood Cells (Human)) were made more difficult because the entry of the bottle introduced the hazard of bacterial contamination and because suitable centrifuges had not been developed.

I participated in the development of refrigerated blood bank centrifuges having personally hounded the industry for at least five years before the first model was demonstrated. In the interim those of us who were convinced of the advantages of using packed red blood cells (PRBC) relied on gravity. Mollison in 1951 recom-

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mended the removal of 200 to 250 ml of citrate plasma from blood stored for 2 to 5 days for use in exchange transfusions of infants with hemolytic disease.[26] We had adopted this technique previously using PRBC adjusted to hematocrits between 60 and 65 per cent and reported our results at the AABB annual meeting in 1950.[14] Based on our very favorable results few exchange transfusions with whole blood were ever performed in Milwaukee during my term as Medical Director of the Milwaukee Blood Center (1947–1966).

Development and Preparation of Blood Components

It remained for Carl W. Walter, a surgeon, to introduce the flexible plastic blood collection bag which was to become the basis of modern component transfusion therapy.[35, 36] The multiple plastic bag, the refrigerated centrifuge, and the differing densities of the plasma and the formed elements have made it possible to separate and concentrate them in a closed system. Using triple or quadruple bags, platelet-rich plasma may be separated by controlled centrifugation within four hours of collection from blood which has not been refrigerated and transferred to a satellite bag. The residual red blood cells (PRBC) in the primary collection bag have the same storage limits and gas-transport function as the original whole blood.

Platelet concentrate, which contains 60 to 80 per cent of the platelets in whole blood, is produced by centrifugation of the platelet-rich plasma and transfer of most of the supernatant platelet-poor plasma to another satellite pack. The platelet-poor plasma must be frozen solid within six hours after collection of the blood if it is to be used as fresh frozen plasma or converted to cryoprecipitated antihemophilic factor. The latter is made from fresh frozen plasma by slow thawing at 4° C, allowing the albumin and most globulins to go into solution leaving the cold (cryo-) insoluble proteins in suspension. The cryoproteins representing 40 to 65 per cent of the antihemophilic factor (Factor VIII) and about one-third of the fibrinogen are separated by centrifugation and stored frozen in 10 to 15 ml of the autologous cryo-poor plasma. The remainder of cryo-poor plasma is transferred to another satellite pack in which it can be stored frozen for use as a volume expander when Factor VIII is not needed, for the perfusion of organs prior to transplantation and also for the management of patients with Factor IX deficiency (hemophilia B, Christmas disease) or prothrombin complex deficiencies because the prothrombin complex factors (Factors II, VII, IX and X) are preserved. The cryo-poor plasma may also be pooled with other plasma for eventual fractionation into albumin and gamma globulin.

The major advantages of using the components of blood just described over whole blood are: (1) the ability to achieve effective therapeutic levels of the component given because of the smaller volume; (2) significantly less hazard of circulatory overload; (3) more effective utilization of the available blood supply; and, most important, (4) better overall clinical effectiveness.[33]

Packed Red Blood Cells: The Backbone of Component Transfusion Therapy

The use of red blood cell concentrates (PRBC) deserves special attention because this component is the most frequently used and because unless the usage of PRBC reaches the desirable goal of 80 to 90 per cent of all transfusions it will not be possible to meet the ever increasing demand for the other components. Keep in mind whenever you think of ordering whole blood that you may be depriving not only your patient but several others of the benefits of component transfusion.

It has been established that units of PRBC with hematocrits exceeding 80 per cent survive in the circulation and function as well as red cells from whole blood during the entire permissible period of storage.[11, 12] The advantages of PRBC over whole blood are that the same dose of red cells is given in half the volume and contains 35 to 40 mEq less of sodium ions, less citrate and less detritus from disintegrating platelets and leukocytes.[3] For these reasons the dictum is that 80 to 90 per cent of all blood transfused should be PRBC in the interest of the patients. In 1976 as high as 86.7 per cent of blood distributed by some Red Cross Regional Blood Centers was in the form of PRBC. The reported average for the almost five million units supplied by the Red Cross was 50 per cent, which is lower than the true proportion because many hospital blood banks remove plasma from whole blood

delivered to them without our knowledge. By 1980 it is almost certain that the use of whole blood for transfusion will be as rare as the shotgun prescription of days of yore.

The most frequently heard objection to the use of PRBC in the operating room is the higher viscosity. This is readily overcome by adding 50 to 100 ml of noncalcium containing iso-osmotic solution through the ubiquitous Y-recipient set and mixing before starting each unit.

I do not want to create the impression that I favor the use of blood in any form during surgery. Certainly the safest blood transfusion is the one that is not given, especially to an obtunded patient. A surgical expert on shock has recently written, "Acute hemorrhage of two liters or less in an adult can usually be treated without whole blood. Given a satisfactory blood volume, hematocrit values of 30% or more are not associated with symptoms and, in many patients, values in the high or even mid 20's are well tolerated. There is no good evidence that physiologic functions, anesthesia, recovery from trauma or operations, or wound healing are adversely affected by anemia. Exceptions are patients with cardiovascular or coronary insufficiency, myocardial damage, or severe respiratory failure." He also states, "In fact, whole blood should be used sparingly and often can be avoided altogether as one becomes knowledgeable and experienced in the use of substitutes and blood components. One must consider the following: First, shock is rarely caused by anemia. Volume can be effectively restored by the administration of either colloids or saline solutions."[15] The writer agrees and has quoted extensively in the belief that surgeons speak more effectively to other surgeons. At this point it should hardly appear unreasonable to urge that when blood is needed during surgery at least the first two units given should be PRBC.

Massive Transfusions

Acute blood loss equal to or exceeding a patient's total blood volume is one of the few indications for the transfusion of whole blood. The problems associated with such massive transfusions cannot be discussed completely here. In his excellent review of the subject John Collins,[7] a surgeon, presents evidence that the impact of blood replacement with bank blood is likely to be less when more blood is used early. He correctly points out that giving acidic whole blood to an acidotic patient usually results in alkalosis because the citric and lactic acids involved are rapidly metabolized when tissue perfusion is restored releasing the bound base. One of the problems associated with massive exchange transfusions with red cells stored for longer than 14 days is the increased affinity of the hemoglobin for oxygen caused by the metabolic loss of 2,3-diphosphoglycerate (DPG) and a fall in the P50 value.* Collins' observations show that even total transfusions with one or two blood volumes of stored blood with low DPG levels the P50 usually remains above 20 mm Hg. It has also been shown that the DPG levels and the P50 values of transfused donor cells are significantly restored 4 hours after infusion.[1, 32] Lowering of the blood pH causes a shift of the oxygen dissociation curve to the right, which means that the release of oxygen by hemoglobin is improved counterbalancing the increased affinity caused by lowered DPG values. For the reasons given above the use of alkalinizing solutions is not indicated and in fact may make the oxygen delivery by red cells with lower than ideal DPG levels less efficient.

Another frequently expressed but rarely substantiated concern is the possibility of bleeding due to dilution of the platelets and plasma clotting factors by replacement with stored blood.[30] Dilutional thrombocytopenia with platelet counts as low as 50,000 per μl, which is at the borderline of safety, is uncommon.[7] The most labile of the clotting proteins, Factor VIII, is usually at least 30 per cent of normal after storage of blood for 21 days.[13, 19] In hemophiliacs the therapeutic goal is to raise the Factor VIII level to 30 per cent, so that lowering to critical levels by replacement with stored blood would be expected to be nearly impossible. The other coagulation factors are more stable than Factor VIII. In routine practice it is generally recommended that a unit (250 ml) of fresh frozen plasma be given after every four to five

*P50 is the oxygen tension in mm of mercury at which hemoglobin is half saturated at 37° C and pH 7.4—the normal value is 26 mm Hg.

units of bank blood.[16] Platelet concentrates are occasionally useful, especially when using an extracorporeal shunt which may damage the patient's own platelets.

Extracorporeal Shunts

The introduction of the cardiopulmonary bypass added a new dimension to problems of blood banking. At first fresh heparinized blood and intercrossmatch of all the donors were demanded. It is worth discussing both of these misconceptions because of their importance to clear historical perspective.

From the time that heparin was discovered by McLean[24] in Howell's laboratory in 1916 it has been the mistaken belief of many that it accounted for the fluidity of blood. Thus heparin has had a special appeal as an anticoagulant. It may therefore come as a surprise that it was not until 1954 that a heparin-like anticoagulant could be demonstrated in normal plasma.[27] Heparin added in vitro may damage platelets but it is not certain whether it inhibits or potentiates platelet function.[34]

The demand for fresh heparinized blood created serious logistical problems for blood banks, especially since heparinized blood has to be discarded after 48 hours. The magnitude of the problem led the concerned group to request the National Academy of Sciences–National Research Council to organize a conference on the subject of "priming the pump." The conference was held in June, 1965, under the sponsorship of the Committee on Blood and Blood Transfusion, Division of Medical Sciences, NAS-NRC.[2] It was concluded that there is little difference between acid-citrate-dextrose (and now citrate-phosphate-dextrose) and heparinized blood. After this conference there came about gradual acceptance for use in pump oxygenators of routinely collected bank blood modified by the addition of heparin followed by recalcification up to 5 days after collection. Now the manufacture of containers with heparin anticoagulant has almost stopped. Improved techniques have made it possible to use red cells previously held in frozen-storage,[31] and some centers use a no-blood prime supplemented by PRBC, cryoprecipitate, or fresh frozen plasma as indicated and no whole blood.[22]

It may be hard to believe now but it is true that some early workers felt it necessary to perform crossmatches between each donor as well as with the patient. This meant doing 400 to 625 additional crossmatches when 20 to 25 donors were used. This was done in spite of the advice of expert blood group serologists that screening of each donor's serum for antibodies and the usual crossmatch with the patient was sufficient.

Happily the days of fresh heparinized blood and intercrossmatches are now a matter of history. The difficulties were in part the result of insufficient communication and teamwork. Surgeons, anesthesiologists, and transfusionists have to work more closely to utilize most effectively the advances occurring in each field. The blood bank should not be thought of as a grocery store but as a source of valuable consultation in hemotherapy.

It is important for the surgeon and the anesthesiologist to have at least a working familiarity with what is available for their patients. When you have a bleeding problem, the modern answer is not necessarily the administration of fresh whole blood, although occasionally it may be. Consultation with the blood bank director and identification of the specific deficiency are essential. Waiting for freshly collected blood may delay and complicate management of the patient. It would be impossible to raise Factor VIII to therapeutic levels without using some form of concentrate (cryoprecipitate, 70 to 100 AHF units per 10 to 15 ml; lyophilized AHF concentrate, 250 AHF units per 10 ml). Cryoprecipitate is useful in managing von Willebrand's disease[6] and is also the safest source of fibrinogen in the rare circumstances where it is indicated. Each pack of cryoprecipitate contains 200 to 250 mg of fibrinogen.[17, 29] Platelet concentrates should have more than 5.5×10^{10} platelets in 20 to 50 ml of plasma depending on the type of preparation; thus the number of platelets found in 4 liters of blood can be administered in a volume of from 160 to 400 ml. This is the usual dose for a 70 kg patient and ideally should raise the platelet count by approximately 40,000 to 60,000 per μl.

Improving the Ordering of Blood for Surgical Procedures

It is imperative to deliver the best care at the lowest cost possible. A situation exists which not only leads to wastage but also escalates cost. It arises from the

routine crossmatching of blood for procedures which rarely require transfusion. For example, in one report 213 units of blood were crossmatched for 97 patients undergoing cholecystectomy and only 5 were used—a crossmatch to transfusion ratio of 42.6.[25] When this single example is extrapolated to the national scale of 432,000 cholecystectomies performed in 1974, it becomes apparent that vast amounts of effort and money could be saved by lowering the average crossmatch to transfusion ratio. These authors advocate replacing the preoperative crossmatch with typing and screening the patient for unexpected antibodies in all procedures shown to require less than an average of 0.5 units of blood (PRBC) per patient.[4, 25] Another recent paper addressed this problem by establishing a maximal surgical blood order schedule (MSBOS) based on actual previously established average usage for each procedure.[10] In either case adequate blood is available in reserve without crossmatching, and in an emergency when the surgeon cannot wait 45 minutes for completing the regular crossmatch procedure, abbreviated procedures which will permit release in 15 minutes can be used.

Conclusion

At one time magic properties were ascribed to blood transfusions and the blood of a docile lamb was believed to calm a violent insane patient—and well it might have, permanently. Samuel Pepys, after hearing of an experiment in which "transfusing the blood of one dog into another was made . . . upon a little mastiff and a spaniel with good success, the former bleeding to death, and the latter receiving the blood of the other, and emitting so much of his own, as to make him capable of receiving that of the other" remarked in his diary on November, 1666 that, "This did give occasion to many pretty wishes, as of the blood of a Quaker to be let into an Archbishop, and such like."[9]

For a long time we were enslaved by the routine and almost reflex use of whole blood for transfusion because nothing else was practical. Now we can give the specific component the patient needs in adequate quantities with much less risk.

I trust that putting some of the problems and progress in blood transfusion therapy (hemotherapy) under the magnifying lens of historical perspective will be useful in dispelling "many pretty wishes" and frustrating misconceptions.

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